RELATIONSHIP OF EXPOSURE TO TOXIC CHEMICALS AND REPRODUCTIVE IMPAIRMENT

HEARING

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

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U.S. HOUSE OF REPRESENTATIVES

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RELATIONSHIP OF EXPOSURE TO TOXIC CHEMICALS AND REPRODUCTIVE IMPAIRMENT

TUESDAY, JULY 27, 1982

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
Washington, D.C.

The subcommittee met, pursuant to call, at 9:30 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. GORE. The subcommittee will come to order. I would like to welcome all of our witnesses and guests today.

In the early 1960's, not much was known about chemical carcinogenesis. Today, because of the concentrated research effort made during the past decade, the mechanisms of chemical carcinogenesis are starting to become unraveled. Yet, while measurable progress is beginning to be made in the area of cancer research, we still don't understand much at all about another hazard, one as elusive and complex in nature as are the many diseases of cancer. Reproductive impairments, spanning a range of problems from male and female infertility, to miscarriages and premature births, to functional birth defects, are becoming a recognizable public health problem in the United States of significant proportion.

Today, the subcommittee will examine the relationship of exposure of toxic chemicals and reproductive impairment. We will attempt to address a number of difficult scientific and policy questions raised by this subject. How important are reproductive impairments as a public health problem? How reliable are existing methods for identifying chemical hazards to reproduction? What coordination exists between various Government agencies in the identification of reproductive hazards? Last, but most important, what should our agenda be so that we can improve our ability to detect chemicals of potential concern to reproduction.

During the past four decades, the evidence has been steadily accumulating which indicates that exposure to certain chemical agents can result in reproductive dysfunction. In recent years, a number of widely publicized tragedies have dramatically illustrated the severity of the reproductive problems that can be chemically induced.

First, the most disastrous and well known case of environmental poisoning occurred with mercury in Minamata, Japan in the early 1950's. Residents consuming fish from the Minamata River, into which the Chisso Chemical Co. discharged small quantities of chlor-

omethylmercury for several years, soon suffered from degenerative neuropathy. Documented reproductive effects included miscarriages, stillbirths, neurological birth defects, and retardation.

Second, in 1971, the first cases of rare vaginal cancers in female offspring exposed in utero to the antiabortant drug diethylstilbestrol, or DES, were reported.

Third, in 1975, male workers at an agricultural formulating plant in California discovered, over coffee discussions, that no one in the plant had fathered any children for several years. Subsequent medical tests confirmed that the pesticide dibromo- chloropropane, or DBCP, which was manufactured at the plant, caused reversible infertility in the male workers.

The greatest tragedy of all lies in the fact that each of these studies was restrospective in nature. If the reproductive destructiveness of these chemicals had been suspected before human epidemiology confirmed their impact, perhaps the human suffering that transpired could have been avoided.

Today we shall hear about the state of scientific knowledge concerning chemical hazards to human reproduction from a panel of noted experts in the area. We want to know from them how surveillance methods can be improved and what research needs to be done so that we may determine, as early as possible, what chemicals are likely to jeopardize future generations.

We will also hear from the Government research and regulatory agencies—NIOSH, the National Institute for Occupational Safety and Health; NIEHS, National Institute for Environmental Health Sciences; OSHA, Occupational Safety and Health Administration; FDA, Food and Drug Administration; and EPA, Environmental Protection Agency—about their present and projected emphasis in reproductive hazard identification. Most importantly, we will attempt to arrive at a consensus on the scientific basis necessary for regulatory decisions.

The ultimate concern of this subcommittee in this hearing is with the extent of reproductive impairments as a public health problem and the role of occupational and environmental chemicals in exacerbating this problem. The science underlying reproductive hazard identification is only in its infancy. However, we must insure its development into a mature science, just as we must insure the sound maturation of our future generations.

I will at this point invite the members of our first panel to come to the witness table, Dr. Ian Nisbet, vice president and principal science advisor with Clement Associates, Inc., in Arlington; Dr. Vilma R. Hunt, professor of environmental health with Pennsylvania State University; Dr. Jeanne Manson with the University of Cincinnati Medical School; Dr. Vasilios Frankos, associate director of the Life Sciences Division, Clement Associates; and Dr. Arthur D. Bloom with the department of pediatrics and human genetics and development, College of Physicians and Surgeons, Columbia University.

Ladies and gentlemen, if you would come forward to the witness table.

I would like to welcome all of the witnesses on the first panel. Dr. Hunt, this is your second visit to the subcommittee, and we certainly appreciate your help on this issue. Dr. Bloom, I wish to

thank you for all of the work that you have done on the issue of genetic screening, chairing the OTA Panel on the subject that has been of so much concern to the subcommittee.

I think that we will begin with Dr. Nisbet, vice president and principal science adviser with Clement Associates, Inc., Arlington, Va.

Without objection, the entire prepared text of all of our witnesses' statements will be included in the record in full. We invite you to go ahead and, if you want to summarize, that is fine; if you want to present it in full and it is not that long, you may.

STATEMENTS OF DR. IAN C. T. NISBET, VICE PRESIDENT AND PRINCIPAL SCIENCE ADVISER, CLEMENT ASSOCIATES, INC., ARLINGTON, VA.; VILMA R. HUNT, ASSOCIATE PROFESSOR OF ENVIRONMENTAL HEALTH, PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PA.; JEANNE MANSON, UNIVERSITY OF CINCINNATI MEDICAL SCHOOL, CINCINNATI, OHIO; VASILIOS FRANKOS, ASSOCIATE DIRECTOR, LIFE SCIENCES DIVISION, CLEMENT ASSOCIATES, ARLINGTON, VA.; AND ARTHUR D. BLOOM, DEPARTMENT OF PEDIATRICS AND HUMAN GENETICS AND DEVELOPMENT, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK, N.Y.

Dr. NISBET. Mr. Chairman, it is a great privilege to be here. I appreciate your invitation to present testimony.

My name is Ian Nisbet. I am vice president of Clement Associates, which is a science and engineering consulting firm in Arlington, Va. Clement Associates specializes in assessing health and environmental risks posed by toxic chemicals in the environment, and I am responsible for the overall scientific qualify of the work done by the firm.

I am testifying today about Clement's work in assessing effects of toxic chemicals on human reproduction. In July 1980, Clement Associates entered into a contract with the Council of Environmental Quality to prepare a review of scientific knowledge of chemical hazards to reproduction, and to evaluate the policy implications of that scientific knowledge. I directed this review, which was carried out by Clement's scientists and consultants, with considerable input from external reviewers. Our 300-page report, which was entitled "Chemical Hazards to Human Reproduction," was published by CEQ in January 1981. However, I understand that, as a result of the change in administration, this report has not had wide circulation outside the sponsoring agencies. The sponsoring agencies included not only CEQ, but also the Environmental Protection Agency, NIOSH, the National Institute for Environmental Health Sciences and OSHA.

Because of the limited time and resources available for our study, we were not able to make a complete, in-depth review of the entire scientific literature on chemical hazards to reproduction. Specifically, we were able to review scientific data on only about 50 of the best-studied chemical agents. However, our review is was more extensive than any other that we found in the scientific literature. In particular, most previous published reviews had been limited to teratogenic chemicals—that is, chemicals that produce

birth defects—whereas, in our report, we surveyed all types of adverse effects on human reproduction.

I would now like to summarize briefly the findings of our review. First, reproductive impairments of one kind or another are both frequent and widespread in the U.S. population. Problems that appear to affect millions of couples at one time or another include inability to conceive, spontaneous abortions, premature births, low birth weights, morphological or functional birth defects, and perinatal mortality. Published estimates of the proportion of reproductive attempts that fail or are impaired in one or more of these ways range from 30 percent to as high as 80 percent. The higher figures result from the inclusion of failures at conception or immediately after conception. These failures appear to be extremely frequent, but are difficult to detect except when they are manifested as prolonged inability to conceive. This, reproductive impairments appear to be a pervasive and significant public health problem.

Mr. GORE. Can I interrupt you there, Doctor? I know it is unusual in the middle of your statement. Let me ask you about that figure because it is so high. What does that represent?

Dr. NISBET. That represents the proportion of instances of unprotected intercourse at the time of a woman's fertility that do not result in a life birth. That includes failures to conceive—for one reason or another—failures of implantation, early embryonic deaths—which are not usually detected except perhaps as missed periods—and the more familiar types of reproductive impairments which include spontaneous abortions, late miscarriages, stillbirths, postnatal mortality, low birth rate and birth defects, some of which don't become apparent until adolescence.

Mr. GORE. I will explore that more in the questioning. Excuse me for interrupting.

Dr. NISBET. The second finding of our review was that existing sources of statistical information on reproductive impairment are not sufficient to serve as a useful basis for investigation of their causes. The National Center for Health Statistics compiles records of births and deaths that are collected by the States. These vital statistics include reliable and complete data on births, birth weights, and infant mortality.

However, these records do not include, for example, the data on occupations of both parents that would be necessary to establish linkage of adverse effects with chemical exposures. Data on adverse outcomes such as miscarriages and birth defects are variable and usually incomplete. For example, one study indicated that the NCHS data on birth defects included only between one-tenth and one-twentieth of the total number of congenital and developmental abnormalities that are identified. No statistical data of any kind are compiled on other major types of reproductive impairment, such as infertility, inability to conceive, and early miscarriages.

Despite the limitations of the national statistics, some significant statistical patterns can be identified. For example, the frequency of birth defects shows much greater variability from State to State, and even from county to county, that can be explained by inconsistencies in reporting. The frequency of two types of congenital defects, anencephaly and spina bifida, in New York and New England increased greatly during the period 1925 to 1950, and has

since decreased again. These spatial and temporal patterns suggest that environmental factors that vary in space and time play a significant role in causing birth defects.

Our third finding was that a number of environmental agents, including chemicals, have been associated with adverse reproductive outcomes in humans. These agents include a number of therapeutic drugs, alcoholic beverages, cigarette smoking, various illicit drugs, and a number of industrial chemicals to which men and women are exposed in the workplace. The best documented examples include thalidomide, diethylstilbestrol or DES, alcoholic beverages, cigarette smoking, anesthetic gases, dibromochloropropane, kepone, lead, and other emissions from metal smelters.

We found no documented association between reproductive impairments and environmental pollutants, such as water pollutants or pesticide residues. However, this finding is of extremely little significance because no studies designed to detect such an association have yet been reported.

Our fourth finding was that there is a fairly good correspondence between adverse reproductive effects observed in humans and those observed in experimental animals exposed to the same chemicals. We derived this conclusion from a review which we conducted of scientific data for 24 chemicals that were known to impair human reproduction. In each case, we found that data existed for at least one experimental animal species which showed similar effects to those observed in humans. We found that animal data matched human data not only for birth defects—as has been pointed out in previous reviews—but also for other types of impairment such as male infertility and fetal death.

Furthermore, we found that in most cases there was a fairly good quantitative correspondence between the doses required to cause effects in humans and animals. Specifically, we found that humans were generally a little more sensitive than the most sensitive animal species when doses were expressed in comparable units.

Although these results are preliminary, they have important implications for our ability to conduct risk assessments. For example, an assumption that humans are likely to respond to a dose 5 times larger than the doses that affect the most sensitive species of experimental animal would provide a reasonable qualitative and quantitative prediction of the effects of the 24 chemicals studied by us, with a margin of safety in some cases.

However, before recommending this assumption as the basis for risk assessments, it needs to be clarified whether this assumption would generate many "false positive" predictions of hazard. Some chemicals, such as aspirin and caffeine, have been known to have adverse effects on reproduction on mammals at fairly high doses, but are not yet known to have comparable effects in humans. We recommended in our report that a more systematic study should be made of the feasibility of using animal data in this way for qualitative and quantitative risk assessment.

However, in spite of this recommendation for further study, we regard our preliminary results as highly promising.

Our report finally addressed the policy implications of our scientific results. First, as I have already said, reproductive impairments

appear to be a pervasive and significant public health problem. Second, there is evidence that drugs, workplace chemicals, alcohol, and cigarette smoking contribute significantly to this problem in groups exposed to them. Third, there is preliminary evidence that experimental studies in animals can serve as the basis for quantitative assessment of reproductive risks.

In our report, we drew a parallel between the state of knowledge of reproductive impairment in 1980 and that of cancer in the late 1960's. In both cases, the magnitude of the public health problem was recognized, some environmental cases had been identified, and the basis for a system of risk assessment had been established in a preliminary way. Although it is not yet clear that chemical hazards to reproduction will prove to be as large a public health issue in the 1980's as chemical carcinogens were in the 1970's, we recommended that research programs should be focused on these critical issues before they become public controversies.

Mr. Chairman, I appreciate the opportunity to present our scientific work to you, and I will be glad to answer questions.

[The prepared statement of Mr. Nisbet follows:]

TESTIMONY OF IAN C. T. NISBET, PH. D.

Mr. Chairman and Members of the Subcommittee, I greatly appreciate your invitation to present testimony here today.

My name is Ian Nisbet. I am Vice President and Principal Science Advisor of Clement Associates, a science and engineering consulting firm located in Arlington, Virginia. Clement Associates specializes in assessing health and environmental risks posed by toxic chemicals in the environment, and I am responsible for the overall scientific quality of its work.

I am testifying today about Clement's work in assessing effects of chemicals on human reproduction. In July, 1980, Clement Associates entered into a contract with the Council on Environmental Quality (CEQ) to prepare a review of scientific knowledge of chemical hazards to reproduction, and to evaluate the policy implications of this knowledge. I directed this review, which was carried out by Clement's scientists and consultants, with considerable input from external reviewers. Our 300-page report, entitled "Chemical Hazards to Human Reproduction," was published by CEQ in January, 1981. However, I understand that, as a result of the change in administration, it has not had wide circulation outside the sponsoring agencies, which included the Environmental Protection Agency, the National Institute for Occupational Safety and Health, the National Institute of Environmental Health Sciences, and the Occupational Safety and Health Administration.

Because of the limited time and resources available for our study, we were not able to make a complete, in-depth review of the scientific literature on chemical hazards to reproduction. Specifically, we were able to review scientific data on only about 50 of the best-studied agents. However, our review is more extensive than any other that we found in the scientific literature. In particular, most previous reviews have been limited to teratogenic chemicals—that is, chemicals that produce birth defects—whereas we surveyed all types of adverse effect on human reproduction.

I would now like to summarize briefly the findings of our review. First, reproductive impairments of one kind or another are both frequent and widespread in the U.S. population. Problems that appear to affect millions of couples at one time or another include inability to conceive, spontaneous abortions, premature births, low birth weights, morphological or functional birth defects, and preinatal mortality. Published estimates of the proportion of reproductive attempts that fail or are impaired in one or more of these ways range from 30 percent to as high as 80 percent. The higher figures result from the inclusion of failures at or immediately after conception. These failures appear to be extremely frequent, but are difficult to detect except when they are manifested as prolonged inability to conceive. Thus, reproductive impairments appear to be a pervasive and significant public health problem.

Our second finding was that existing sources of statistical information on reproductive impairment are insufficient to serve as a useful basis for investigation of their causes. The National Center for Health Statistics (NCHS) compiles the records of births and deaths that are collected by the states. These vital statistics include

reliable and complete data on births, birth weights, and infant mortality. However, these records do not include, for example, the data on the occupations of both parents that would be necessary to establish linkage of adverse effects with chemical exposures. Data on adverse outcomes such as miscarriages and birth defects are variable and usually incomplete. For example, one study indicated that the NCHS data on birth defects include only between one-tenth and one-twentieth of the total number of congenital and developmental abnormalities that are identified. No statistical data are compiled on other major types of reproductive impairment, such as infertility, inability to conceive, and early miscarriages.

Despite the limitations of the national statistics, some significant statistical patterns can be identified. For example, the frequency of birth defects shows much greater variability from state to state and even from county to county than can be explained by inconsistencies in reporting. The frequency of two types of congenital defects—anencephaly and spina bifida—in New York and New England increased greatly during the period 1925–1950, and has since decreased again. These spatial and temporal patterns suggest that environmental factors that vary in space and time play a significant role in causing birth defects.

Our third finding was that a number of environmental agents, including chemicals, have been associated with adverse reproductive outcomes in humans. These agents include a number of therapeutic drugs, alcoholic beverages, cigarette smoking, various illicit drugs, and a number of industrial chemicals to which men and women are exposed in the workplace. The best documented examples include the following:

Thalidomide—a drug which was used for a short period around 1961 and which caused 7,000–8,000 cases of major congenital abnormalities world-wide before it was identified and withdrawn from the market.

Diethylstilbestrol (DES)—a drug which was used for a long period to prevent miscarriages, but which has led to abnormal development of the reproductive organs in many thousands of the offspring of the treated women, including cancer in a few of their daughters.

Alcoholic beverages—which cause a distinctive pattern of birth defects in the offspring of heavy drinkers, and reduced birth weights and spontaneous abortions in moderate and light drinkers.

Cigarette smoking—which is associated with a wide range of adverse effects on the mother, the fetus, and the newborn infant.

Anesthetic gases—which are associated with spontaneous abortions in nurses, anesthetists, and other medical personnel, including the wives of exposed males.

Dibromochloropropane (DBCP) and kepone—two pesticides which caused infertility in male workers exposed to them in the manufacturing plants.

Lead and other emissions from metal smelters—which are associated with a wide variety of reproductive impairments in exposed men and women.

We found no documented association between reproductive impairments and environmental pollutants, such as water pollutants or pesticide residues. However, this finding is not significant because no studies designed to detect such an association have been reported.

Our fourth finding was that there is a fairly good correspondence between adverse reproductive effects observed in humans and those observed in experimental animals exposed to the same chemicals. We derived this conclusion from a review which we conducted of scientific data for 24 chemicals that were known to impair human reproduction. In each case, we found that data existed for at least one experimental animal species which showed similar affects to those observed in humans. We found that animal data matched human data not only for birth defects (as had been pointed out in earlier reviews), but also for other types of impairment such as male infertility and fetal death. Furthermore, we found that in most cases there was a fairly good quantitative correspondence between the doses required to cause effects in humans and animals. Specifically, we found that humans were generally a little more sensitive than the most sensitive animal species, when doses were expressed in comparable units (milligrams of chemical per unit of body surface area per day).

Although these results are preliminary, they have important implications for our ability to conduct risk assessments. An assumption that humans are likely to respond to a dose 5 times larger than the doses that affect the most sensitive species of experimental animal would provide a reasonable qualitative and quantitative prediction of the effects of the 24 chemicals studied by us, with a margin of safety in some cases. However, before recommending this assumption as the basis for risk assessments, it needs to be clarified whether it would generate many "false positive" predictions of hazard. Some chemicals, such as aspririn and caffeine, have adverse

effects on reproduction in mammals at fairly high doses, but are not yet known to have comparable effects in humans. We recommended that a more systematic study should be made of the feasibility of using animal data in this way for risk assessment, but we regard our preliminary results as highly promising.

Our report finally addressed the policy implications of our scientific results. First, reproductive impairments appear to be a pervasive and significant public health problem. Second, there is evidence that drugs, workplace chemicals, alcohol, and cigarette smoking contribute significantly to this problem in groups exposed to them. Third, there is preliminary evidence that experimental studies in animals can serve as the basis for quantitative assessment of reproductive risks. We drew a parallel between the state of knowledge of reproductive impairment in 1980 and that of cancer in the late 1960s. In both cases, the magnitude of the public health problem was recognized, some environmental cases had been identified, and the basis for a system of risk assessment had been established in a preliminary way. Although it is not yet clear that chemical hazards to reproduction will prove to be as large a public health issue in the 1980s as chemical carcingens were in the 1970s, we recommended that research programs should be focused on these critical issues before they become public controversies.

I appreciate the opportunity to present our scientific work to you, and I will be glad to answer questions to the extent of my ability.

Mr. GORE. Thank you very much. We will hold up on questions until the panel is all done.

I would like to call next on Dr. Vilma R. Hunt, professor of environmental health, Pennsylvania State University.

Dr. HUNT. Thank you.

I was on leave from the Pennsylvania State University from the period of December 1977 through 1981, during which time I served with the Science Advisory Board of the U.S. Environmental Protection Agency, and spent 2 years as the Deputy Assistant Administrator for Health Research in the Office of Research and Development. Today I speak to you as a private citizen, whose testimony is based upon personal knowledge and professional experience.

I will just comment on some parts of the testimony which you have in full. Particularly, I would call your attention to what I said the last time I appeared before you, and I would like to expand on that a little further. I am particularly concerned with the balance of research as we see it across agencies. The central point is whether we have available to us tests which have been adequately validated. I spoke to that issue, as I said, last time.

Validation, as a general concept, covers the progression from short-term bioassays or animals tests to a stage where those observations can be confidently extrapolated to the human condition. Ideally, in the case of testing for possible toxic effects, we can make qualitative and quantitative observations of the biological responses common to short-term tests, animal tests, and tests on human populations. As Dr. Nisbet said, we will not develop any better confidence in risk assessment until this chain of data is improved.

We seldom have the ideal situation to complete that chain and, fortunately, the Toxic Substances Control Act contains a section which precludes exposure of human populations to unknown chemicals without testing for safety. This provision, of course, prevents the progression of a validation process all the way to clinical and epidemiologic studies on humans, to prove that what the laboratory studies showed was correct.

So far, despite the millions of research dollars we have expended over the past 20 years, we can only trace the validation process for

toxic substances in high exposure situations. That has been in the Minamata disease situation, kepone poisoning, and situations of that kind. I couldn't resist the footnote that I have put there, because I still feel that the Borgias did very well in the 15th century Italian courts because they knew that much toxicology already.

We have not applied sufficient research effort to conditions of low-dose, long-term exposure. For example, the lead standard cites one study of effects on sperm integrity and male reproduction done by Elana Lancranjan on Romanian leadworkers, published in the Archives of Environmental Health, a referred American journal. The study has been intensively scrutinized. Dr. Lancranjan was brought from Europe to testify at the OSHA hearings on the lead standard; but today, more than 7 years later, no confirmatory studies have been published that I am aware of. This means that the questions raised by such a pioneering, first-time, flawed study still hang in midair.

These authors did a similar study on microwave exposure—an area I know you are interested in—also published in an American journal, referred, "Health Physics." I have heard scientists reject these studies out of hand, because they were carried out in Eastern Europe where research protocols are often less stringent than here—and I might add not published in American journals—but I have never heard the expected corollary comment: These studies should be repeated and confirmed or refuted, because they are important and crucial to the validation process which rests on the basic research of spermatogenesis, short-term test development and animal toxicology.

The result is that today we cannot readily use a relatively noninvasive approach in assessing a male reproductive effect because we do not know what it means. The female is quite analogous, and that is in terms of menstrual dysfunction, which is an extraordinarily narrow research field, which has not been applied to environmental or occupational toxicology in the United States. Yet, it provides a window on the crucial issue of hormonal balance and uterine function that relates to the reproductive system overall, which may well turn out to be the key to our ultimate understanding of reproductive integrity and the wide variety of responses to toxic substances that the reproductive system presents.

So I reemphasize the crucial point that progress from basic research on the reproductive system to development of appropriate testing procedures for the identification of the toxic effects of a chemical, through to the validation of those tests and their application to situations of particular concern to regulatory agencies must be consistently supported and evaluated.

Research dollars alone are not enough. Research planners and scientists must pay attention to the current research imbalance where the light weight is on the validation end. Research dollars will continue to be wasted if they are lavished only on adaptation of basic research to develop short-term tests without an equally strong commitment to insuring that those tests will be valid and appropriate for decisions by policymakers and regulatory agencies and for a scientific response to the public's right to know.

I have commented on the history of the recent years in relation to reproductive health, and I have appended a historical bibliogra-

phy which will provide you with the reports that have been developed since 1975. I also added to that the funding sources as well as I knew them under the information available to me. They do provide, I believe, a very good overall assessment of where we stand in the reproductive area right now. We have absolutely no excuse for saying that we do not know what research should be done and what research is of high priority in this area. There is a plethora of information available to us all. Many of us in this room have been working together for years on this, and we all know of what I speak.

I would then like to wrap up my testimony here just commenting directly to you. First of all, commenting on the importance of the most recent document—and I am pleased to see Dr. Bloom here. I guess it is the book that is going to be called the "Yellow Book" at the March of Dimes. I have spoken more directly to it in my testimony, but I do believe that that is a landmark publication. It does bring together much of the information that I spoke to. I believe that, for the first time, the realities of scientists' and physicians' professional responsibilities and limitations are conveyed to the reader. Participants, contributors, and reviewers came from the regulatory and research agencies, industry and academia, and for my money, the publication represents the clearest picture of the state of the art to this date, with all its limitations. The fact that the events of Love Canal had to happen to bring this about has to be sadly acknowledged.

I would say that 1981 is a landmark year in another respect. There have been administrative changes in many agencies, budget stringency and a change in the regulatory climate demand a reassessment of agency relationships, the availability of scientists and the overall coordination of a diffuse, complex research effort.

First, the agency relationships. During the past 5 years, research planning and administration moved beyond the immediate narrow confines of each agency, and there was an intense interaction of scientists and administrators under the auspices of the Interagency Regulatory Liaison Group and the national toxicology program. The IRLG is no more, and the NTP has become a formally constituted permanent program in the Department of Health and Human Services. Reproductive planning issues, I believe, came to be well understood within the regulatory agencies under the IRLG umbrella, due to regular sharing of information, conferences and an overall cooperative climate.

Of course, in a loose consortium without a budget, some of the usual competitive stresses were absent, which brings me to the second point of availability of scientists and the quality of their professional lives. We must maintain the morale and quality of scientists in Government laboratories. In the area of reproductive research, the Federal scientists are first class—at EPA's Research Triangle Park, FDA's National Center for Toxicological Research, and those at the National Institutes of Health and NIOSH.

The perception and professional skill that these scientists bring to the diversity of reproductive problems affects the overall quality of research, not only in the Federal laboratories, but in the universities as well. If they cannot convey to the larger scientific community the overall pattern of research planning and priorities upon

which regulatory agencies must ultimately rely, we will continue to have black holes and black boxes where there should be reliable data.

With the demise of IRLG and severe restrictions of travel funds, I am particularly concerned that the collaborative and cooperative climate within the Federal scientific commun'ty not be eroded. In general, these scientists in the reproductive area of research are at the peak of their research careers. They are a wave of young, mature investigators with good publishing records—not diverted from their central research interests by university teaching and administration which so severely affects academic research. They have 20 years or more of productive research activity ahead of them. I believe that it is not generally realized by the professors who trained them, nor by the administrators who govern their professional lives, what a valuable national resource they are.

But they cannot remain a productive, efficient, and creative force in reproductive research if there is not a constant effort to maintain a stable budget—which is their administrative burden—insure collaborative interaction and build professional morale. As a group, they are the beacon for the next 20 years of research in the reproductive area. I firmly believe that together with the academic community, advances in the understanding of reproductive hazards, and the best means of protecting the procreative integrity of the Nation will flow through their laboratories if you, Mr. Gore, and your congressional colleagues can insure a level of reliable, consistent support, at least comparable in quality to the past 20 years' support for cancer.

[The prepared statement of Dr. Hunt follows:]

STATEMENT OF VILMA R. HUNT, PROFESSOR OF ENVIRONMENTAL HEALTH, THE PENNSYLVANIA STATE UNIVERSITY

I am Vilma R. Hunt. I am professor of Environmental Health at the Pennsylvania State University, where I have been on the faculty since 1969. From December 1977 to May 1981, I was on leave to serve with the United States Environmental Protection Agency—for one year with their science Advisory Board, and for almost two years as the Deputy Assistant Administrator for Health Research in the Office of Research and Development. Today I speak to you as a private citizen, whose testimony is based upon personal knowledge and professional experience.

I testified before this subcommittee on October 15 of last year at which time you were concerned with medical and genetic screening of workers. I dealt with those issues related to reproductive hazards in the workplace and also emphasized the problems inherent to the validation of screening tests and to the subsequent development of scientific consensus and policy formulation. I also brought to your attention the difficulty in assuring that federal funding for research on the reproductive system—basic as well as applied—would be appropriately allocated and I warned that if validation of potential tests and study designs continues to receive the same low priority funding of the past, Love Canal fiascos will continue.

We continue to see in the daily newspapers that such and such study is flawed, or used some inappropriate procedure, or has not been confirmed, so that conclusive results cannot be drawn. A Good Housekeeping Seal of Approval for screening does not exist in the scientific arena, despite the fact that public confidence is being continually eroded by our inability to develop an adequate validation process, Workers or people exposed to environmental toxins are often told that no valid test can establish either their exposure to a hazard or its effects, immediate or potential. As scientists, we live with that level or uncertainly all the time. The public (and their antennae—the policy makers) must have assurance that they can place some confidence in the scientific method and the validity of extrapolations from basic research to their day to day concerns and decisions. I would submit that in the environmental, occupational and consumer product area, we are in poor shape, if the com-

pliants of policy makers and the public (as reported in the media) are any indication. That presents a dangerous fiscal environmental for the scientific community, indeed.

Nowhere is this more evident than in problems associated with reproduction. From pesticide manufacture and use to hazardous dumps, public concern about sterility, impotence, miscarriages, congenital deformities, premature birth, has hit the news. In only a few instances has there been scientific accord that the concerns could be substantiated, the foremost example being the effects of dibromochloropropane (DBCP) on male sterility which was based on clinical observation, not toxicologic evidence based on a validated testing procedure.

And I am hard put to retrieve another example. Even the anesthetic gas studies relating operating room exposure to miscarriage and other effects are "flawed,"—they are epidemiologic studies and never has there been an epidemiologic study done that is not "flawed."

Validation as a general concept covers the progression from short term bioassays or animal tests to a stage where those observations can be confidently extrapolated to the human condition. Ideally, in the case of testing for possible toxic effects, we can make qualitative and quantitative observations of the biological responses common to short term tests, animal tests and tests on human populations. We will not develop any better confidence in risk assessment, for example, until this chain of data is improved. We seldom have the ideal situation to complete that chain and fortunately, the Toxic Substances Control Act contains a section which precludes exposure of human populations to unknown chemicals without testing for safety. This provision, of course, prevents the progression of a validation process all the way to clinical and epidemiologic studies on humans—to prove that what the laboratory studies showed was correct. So far, despite the millions of research dollars we have expended over the past 20 years, we can only trace the validation process for toxic chemicals in high exposure situations,[1] e.g. Minamata Disease for mercury poisoning, kepone poisoning.

We have not applied sufficient research effort to conditions of low dose, long-term exposure. For example, the lead standard cites one study of effects on sperm intergrity and male reproduction done by Elena Lancranjan on Rumanian lead workers, published in the Archives of Environmental Health, a referred American journal. The study has been intensively scrutinized, Dr. Lancranjan was brought from Europe to testify at the OSHA hearings on the lead standard, but today—more than 7 years later—no confirmatory study has been published (that I am aware of). This means that the questions raised by such a pioneering, first-time, "flawed" study still hang in mid-air. These authors did a similar study on microwave exposure, also published in an American Journal—Health Physics. I have heard scientists reject these studies out of hand—because they were carried out in Eastern Europe, where research protocols are often less stringent than here (and I might add, not published in American journals). But I have never heard the expected corollary comment—these studies should be repeated and confirmed or refuted; because they are important and crucial to the validation process which rests on the basic research of spermatogenesis, short term test development and animal toxicology. The result is that today we cannot readily use a relatively non-invasive approach in assessing a male reproductive effect because we do not know what it means. A female example (or many), is unfortunately quite analogous. Menstrual dysfunction is an extraordinarily narrow research field, which has not been applied to environmental and occupational toxicology in the United States. Yet it provides a window on the crucial issue of hormonal balance and uterine function that relates to the reproductive system overall, which may well turn out to be the key to our ultimate understanding of reproductive intergrity and the wide variety of responses to toxic substances that the reproductive system presents. The linkage is not anywhere near as complete as the spermatogenesis chain and appears never to have been seriously considered as being part of the total reproductive cycle in the environmental research community.[2]

So I re-emphasize the crucial point—that progress from basic research on the reproductive system to development of appropriate testing procedures for the identification of the toxic effects of a chemical, through to the validation of those tests and their application to situations of particular concern to regulatory agencies must be consistently supported and evaluated. Research dollars alone are not enough. Research planners and scientists must pay attention to the current research imbalance

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[1] No great advance when the Borgias already knew that in the toxic environment of Italian courts of the 15th century.

[2] Half a million years of the menstrual taboo should be taken into account.

where the light weight is on the validation end. Research dollars will continue to be wasted if they are lavished only on adaptation of basic research to develop short-term tests without an equally strong commitment to ensuring that those tests will be valid and appropriate for decisions by policy makers and regulatory agencies and for a scientific response to the public's right to know.

It is appropriate, I believe to recall the brief and recent history of research on the reproductive system, because it may provide some insight into the reasons why we must plan well for the optimum use of scarce research dollars. The comparison will be with cancer research, which for the past 25 years or so has held prime attention, in part related to public concern and successful lobbying and in part related to the rapid advances in research methods, with a very intense feed-back system operating. Dollars have not been a limiting factor. In contrast, interest in reproductive effects during most of that same period, up to 1975, was confined to the United States Atomic Energy Commission and its successor agencies, (and NASA's concern for sperm integrity of astronauts), and the Food and Drug Administration's drug testing program. Basic research was going on in the National Institutes of Health and universities, but research related primarily to contraception, obstetrics and gynecology, and adverse therapeutic drug effects, not to environmental hazards. In 1974, a request for research attention to reproductive hazards came from unexpected source. The Secretaries of Labor and Health, Education and Welfare, were informed by the Women's Equity Action League, that their annual conference had passed a resolution requesting that the departments of Labor and HEW give attention to the reproductive hazards faced by women in dangerous work settings. The office of the Secretary of HEW responded (Ms. Clara Schiffer) and a $2,000 contract was let to prepare a report on "Occupational Health Problems of Pregnant Women." The next year, Congressman Obey's Appropriations Committee added $1 million to the NIOSH (fiscal year 1976) budget for research on male and female reproduction of workers in hazardous jobs. A conference on "Women in the Workplace" was held. The evidence immediately became starkly clear—that there was little, and in many situations, no information in the research literature that was applicable to occupational safety and health deliberations. Policy issues relating to women and their child-bearing capacity which had never been dreamed of, became serious concerns of OSHA, NIOSH, EPA and industry. Then in 1977, the effects of DBCP on male fertility were reported, and the totality of the procreative capacity of men and women was understood for the first time—not just by the women's groups who had to lobby and argue to bring the issue to the attention of federal agencies and Congress—but to scientists and physicians who had not viewed the reproductive system as seriously vulnerable to toxic insult.

Since then, there has been a marshalling of research efforts—as you can now realize—within only the past few years. We do not have the extensive foundation of basic research, scientists and resources that were applied to the cancer problem over the previous 20 years. This recent period has also been a time of change in demographic patterns and parent's expectation. Reduced fecundity and perfect quality control are in the public mind today, so that it may be that federal and state agencies which have to deal with the episodes of DBCP exposure and sterility, Three Mile Island, Agent Orange and Love Canal have taken on the additional load of responding to a heightened public concern for reproductive integrity. The federal response has been a plethora of conferences and reports sponsored by EPA, NIEHS, CPSC, FDA, NTP, OSHA, NIOSH and various combinations thereof, e.g., the report "Chemical Hazards to Human Reproduction" done by Clements Associates for the Council on Environmental Quality (January 1981) was funded by the regulatory agencies, NTP and NIOSH. And the latest, most down-to-earth is the March of Dimes Yellow Book "Guidelines for Studies of Human Populations Exposed to Mutagenic and Reporductive Hazards," (edited by Dr. Bloom) dedicated to the residents of Love Canal. It was funded by EPA, CDC, OSHA, and NIEHS. I believe this publication, based on a conference which brought together a very diverse research community to synthesize into a coherent whole, the accumulated reports and the available reproductive knowledge, will be seen as a landmark in this short history I have recounted. For the first time, the realities of scientists' and physicians' professional responsibility and limitations are conveyed to the reader. Participants, contributors and reviewers came from regulatory and research agencies, industry and academe and for my money, the publication represents the clearest picutre of the state of the art to this date, with all its limitations. The fact that the events of Love Canal had to happen to bring this about has to be sadly acknowledged.

Perhaps 1981 is a landmark year in another respect. Administrative changes in many agencies, budget stringency and a change in the regulatory climate demand a reassessment of agency relationships, availability of scientists and the overall co-

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ordination of a diffuse, complex research effort. First—agency relationships. During the past five years the research planning and administration moved beyond the immediate narrow confines of each agency and their was intense interaction of scientists and administrators under the auspices of the Interagency Regulatory Liaison Group and the National Toxicology Program. The IRLG is no more and the NTP has become a formally constituted "permanent" program in the Department of Health and Human Service. Reproductive research planning issues, I believe, came to be well understood within the regulatory agencies under the IRLG umbrella, due to regular sharing of information, conferences and an overall cooperative climate. Of course in a loose consortium, without a budget, some of the usual competitive stresses were absent, which brings me to the second point of availability of scientists and the quality of their professional lives. We must maintain the morale and quality of scientists in government laboratories. In the area of reproductive research, the federal scientists are first class—at EPA's Research Triangle Park, FDA's National Center for Toxicological Research, and those at the National Institutes of Health and NIOSH. The perception and professional skill that these scientists bring to the diversity of reproductive problems affects the overall quality of research, not only in the federal laboratories, but in the universities as well. If they cannot convey to the larger scientific community the overall pattern of research planning and priorities upon which regulatory agencies must ultimately rely, we will continue to have black holes and black boxes where there should be reliable data. There are now enough conference reports (and contracted summary documents) to provide us with guideposts to the most important research needs.

Additionally, there have been reorganizations which in the case of EPA's Research Triangle Park Laboratory combined the scattered research efforts into one branch which has now been raised to a Division of Developmental Biology. The NCTR group in Reproductive and Developmental Toxicology responds to FDA's needs and coordinates the reproductive toxicology component of the National Toxicology Program and NIOSH has established in fiscal year 1980 a formal reproductive effects initiative, so that in contrast to only three years ago we can readily identify the foci of reproductive research where before such research had been difficult to find and identify. Oak Ridge National Laboratory and other national laboratories of the Department of Energy have participated in many conferences and operate extensive information retrieval systems, but their budgeting allocations to reproductive research have not been as readily availble. I have no knowledge of the extent of such research in the Department of Defense. The National Toxicology Program has taken on two roles: to determine the toxic effects of chemicals and to develop better, faster and less expensive test methods. The program's mandate includes reproductive and developmental toxicology. I would look back to my central theme that validation of those better, faster and less expensive test methods be a continuing concern for all those who administer that program, collaborate with it, advise and have oversight for it. More tests that lead us to the best, useful validated tests is fiscally responsible, more tests which just add to the unsatisfactory non-validated ones we already have, is not. With the demise of IRLG and severe restrictions of travel funds I am particularly concerned that the collaborative and cooperative climate within the federal scientists community not be eroded. In general, these scientists in the reproductive area of research are at the peak of their research careers. They are a wave of young mature investigators, with good publishing records—not diverted from their central research interests by university teaching and administration which so severely affects academic research. They have 20 years or more of productive research activity ahead of them. I believe that it is not generally realized by the professors who trained them, nor by the administrators who govern their professional lives what a valuable national resource they are. But they cannot remain a productive, efficient and creative force in reproductive research if there is not a constant effort to maintain a stable budget (their administrative burden) ensure collaborative interaction and build professional morale. As a group they are the beacon for the next 20 years of research in the reproductive area. I firmly believe that together with the academic community, advances in the understanding of reproductive hazards and the best means of protecting the procreative integrity of the nation will flow through their laboratories. If you, Mr. Gore and your Congressional colleagues can ensure a level of reliable, consistent support comparable in quality[3] to the past 20 years' support for cancer.

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[3] I do not expect dollar quantity.

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FUNDING SOURCES

1. March of Dimes. Birth Defects Foundation.
2. U.S. Consumer Product Safety Commission.
3. United States Department of Energy.
4. United States Environmental Protection Agency.
5. United States Department of Health, Education, and Welfare, Office of the Secretary.
6. United States Department of Health and Human Services. Centers for Disease Control. National Institute of Occupational Safety and Health.
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Mr. GORE. Thank you very much for an excellent statement.

Our next witness is Dr. Arthur D. Bloom, Department of Pediatrics and Human Genetics and Development at the College of Physicians and Surgeons, Columbia University. Dr. Bloom, welcome to our subcommittee. We are familiar with the book referred to earlier, and we invite you to proceed.

[4] Numbers in parenthesis refer to funding sources.

Dr. BLOOM. Thank you, Mr. Gore.

As a geneticist concerned with the interaction between environmental agents and the genetic material of our cells, I wish to distinguish those effects which are induced in germ cells—or reproductive type cells—from those which are induced in somatic, or non-germ cells.

In the case of germ cell effects, we refer here basically to two types of preconception events: First, the exposure may directly alter the sperm or ova of an individual so as to induce a reduction of fertility or frank infertility. Second, heritable alterations may be induced in egg or sperm, and those may be transmitted at conception to the progeny with, at times, clinically detectable genetic disease in the child.

Alternatively, however, when maternal exposure to a reproductive hazard has taken place after conception, then we are dealing with what we call somatic effects, which may result, among other things, in stillbirth, prematurity or congenital malformation. The induction of somatic cell damage which leads to malformation of the embryo or fetus will be referred to here as the teratongenic effect of a physical or chemical agent to distinguish it from the genetic effect of alternations induced in germ cells.

My thesis today will be that while germ cell effects in humans are notoriously difficult to establish, we may reasonably assume that such effects of gene altering or mutagenic chemicals do occur, as do those of mutagenic physical agents like ionizing and perhaps nonionizing radiations. We have, for several reasons, become considerably better at estimating somatic cell effects, such as teratongenicity and carcinogenicity, than we have at estimating true genetic or heritable effects.

The magnitude of this problem may quickly be grasped by a summary consideration of the demonstrated late effects in the Hiroshima and Nagasaki populations. In a sense, the studies of the Hiroshima and Nagasaki survivors have provided us with much of what we know about the effects in humans of exposure to high and low, single doses of a known mutagen and teratogen, namely, ionizing radiation. The dose range was wide enough and the size of the exposed population was large enough to that important lessons could be learned about appropriate approaches to human populations at risk of somatic or genetic abnormalities because of exposure to a potent environmental hazard.

In essence, the major effects described to date in Japan among the A-bomb survivors are essentially somatic effects. That is, numerous types of cancers have been shown to be increased in the survivors, and major effects have been demonstrated in those exposed in utero.

However, virtually all of the studies on those conceived after parental exposure to the A-bomb have been negative. These studies have involved many tens of thousands of such offspring with numerous endpoints having been examined. The endpoints included early miscarriages (spontaneous abortion), congenital malformations, the sex ratio of the progeny and, more recently, chromosomal abnormality and genetically determined biochemical abnormality. In these major manifestations of a possible genetic effect of the ionizing radiation, no increases in these parameters were seen, sug-

gesting that while there may have been such genetic effects induced, their magnitude is such as to render them nondetectable by current technologies.

So, from Hiroshima and Nagasaki comes an important lesson: For a known physical mutagen like radiation, at single high doses, it is not yet feasible to demonstrate heritable genetic effects in humans. We, of course, do not know whether this lesson will apply to chemically-exposed human populations, but it seems to me likely that unless the agent in question is extremely genotoxic, and unless many thousands are exposed, we are likely to continue for the foreseeable future to have trouble proving that any chemical has exerted a "genetic"—heritable—effect in humans.

On the other hand, the post-conception somatic level reproductive studies are more likely to be useful if properly done from an epidemiological point of view. I have mentioned above the major reproductive parameters of congenital malformation, stillbirth and prematurity; but must acknowledge that these may, in fact, be either genetic or somatic, that is, the result of preconception or postconception exposure.

To do these kinds of reproductive studies is often difficult. The exposed populations frequently consist of only a small number of persons; the exposure may produce only rare events, such as a highly specific congenital malformation; and the exposure may be ill-defined, in terms of the agent or agents, the dose, and the duration of exposure.

Two well known recent incidents illustrate some of these difficulties. At Three Mile Island, the estimated exposure dose to persons living within 10 miles of the nuclear plant were, on average, not more than 2 to 3 millirem, a very low radiation dose indeed. We consider 2 to 4 percent of all livebirths are associated with a congenital malformation, so that if there had been 1,000 pregnant women living within that 10-mile radius—there were, in fact, somewhat fewer than that—we would have expected a normal background rate of 20 to 40 abnormalities, congenital anomalies, and even a 10 to 20 percent increase would have unlikely to be detected.

At the Love Canal, the residents were found to have a wide range of chemicals at low concentrations in the basements of their homes. So the situation there was multiple agent exposure over a relatively long period of time. But the small size of the presumably at-risk population, which was in toto about 5,000 persons, would have made it very difficult, though not impossible, to obtain definitive data on parameters such as congenital malformations, spontaneous abortion, and the like.

I have a number of recommendations. First, negative studies. In much of the thinking that has gone on about mutagens in the workplace or in the general environment, there has been a certain reluctance to commit funds and manpower to study workers and their offspring or residents of a geographic area for evidence of reproductive effects when the expectation is that no effects will be found. As in Hiroshima and Nagasaki, the power—social, economic, political and scientific—of a negative study is not to be underestimated, in my view, especially now that we are in the relatively uncertain times of toxic waste dumps and lead nuclear powerplants.

Second, priorities in population research. Were we to try to set population type priorities for proper epidemiological and laboratory studies, we clearly should list as our top priority that population group which has been exposed to high doses of a powerful mutagen. Next, we might wish to study that group which has been exposed to mixtures of known potent mutagens at unknown doses. Last, we might rank that group exposed to low doses or to weak mutagens. In other words, I suggest that we try to set priorities for proper epidemiological and laboratory studies on environmentally exposed human populations, so that reliable data can be collected in a systematic way to inform the scientific community and the public of the nature and type of any effects seen.

Next, newer technologies. These certainly need to be encouraged. Many methods have been developed as part of the continuing search for short-term in vitro or experimental animal test systems. More than 35 such test systems have now been described, but most of them are tests of gene or chromosomal damage in somatic cells, usually nonhuman, and are nor measures of true, heritable mutations passed on from one generation to the next. For inherited mutations, there are primarily mouse colony studies, but extrapolating from mouse to man is neither simple nor satisfying. Thus, new approaches to detection of germinal mutations in man are needed.

The parameters of genetic damage discussed above, such as congenital malformations, are indirect measures of an agent's effect on the genetic material. More direct measures are needed and are, in fact, likely to become available. There are now molecular approaches to induced mutation that appear to be very promising and require support. The principles here involve isolation of DNA from cells, the "cutting up" of the DNA into manageable fragments, and the determination of the sequence of the bases of DNA within the fragments to enable investigators to determine what alterations have taken place directly in the DNA. It is at this time unclear whether this approach will ultimately prove useful for human population monitoring, but it is an approach to molecular mutagenesis which clearly needs encouraging.

Next, population screening and monitoring. This, of course, relates to some of the work that is being done in the OTA Committee on Genetic Screening in the Work Place. The two currently extant approaches to human population studies which may be distinguished are screening and monitoring. We define monitoring in this context as the use of some parameter, such as chromosome damage, as an indicator of exposure. Screening, on the other hand, implies evaluation of the genetic constitution of the individual, as for example, to determine whether the person has a genetic predisposition to develop medical problems under certain workplace conditions.

At present, the two genetic approaches to such testing are, first, cytogenetic, in which chromosome studies are done to look for breakage or rearrangements of normal chromosome structure; and second, biochemical, in which specific normal parameters of metabolism are found to be either simply variant or grossly pathological and resulting in disease. For the most part, it seems that there is little reason to screen humans now, in terms of determining sensitivity to mutagen exposure, since none of the biochemical tests are

really well established as being able to do that, and only a very few cytogenetic tests are thus far promising in this regard.

For monitoring, however, there is some reason to consider using cytogenetic tests in persons suspected of being exposed to genetically toxic chemicals or radiations. The problem is that the presence of chromosomal aberrations may or may not have reproductive implications—chromosomal aberrations in the somatic cells—and there has as yet been no clear example of a person exposed to a genetically toxic agent with somatic damage in him or herself and the preconception exposure to that agent being provable as the cause of genetic disease in the offspring.

So, one of the major research thrusts needed, in my view, is one which will have as its goal the improved monitoring and perhaps screening of human populations for genetic effects of environmental hazards. I do believe that monitoring for reproductive effects is feasible, using a combination of sensitive laboratory techniques and proper epidemiological/statistical study design.

Lastly, the need for an environmental study group on effects. Chemical and physical agents that are mutagenic are ubiquitous in our world. Radiation scientists are concerned about genetic effects; chemically oriented investigators who think about the public health are concerned about genetic effects; and public officials must be concerned, as you obviously are, with the genetic well-being of our species. We require a high-level scientific-governmental body which will begin to formulate research strategies for long-term studies of subsets of our population which are thought to be exposed to mutagens.

We need this research on many levels. We need a systematic exploration of promising laboratory approaches for the detection of mutation. These will include research on biochemical and cytogenetic studies in humans, and research into basic mechanisms of induced mutation. We need expanded research into the clinical genetic effects of environmental agents, that is, research into the ways in which induced genetic alterations express themselves clinically. And, of course, we need much research into the epidemiological study of genetic effects. Population studies of the numerous parameters of genetic damage need greater definition and refinement than they now have.

I would suggest that there is no greater responsibility than the protection of future generations from the environmental problems of today.

Thank you.

[The prepared statement of Dr. Bloom follows:]

STATEMENT OF ARTHUR D. BLOOM, M.D.

Mr. Chairman, Members of the Committee, as a geneticist concerned with the interaction between environmental agents and the genetic material of our cells, I distinguish those effects which are induced in germ cells from those which are induced in somatic, or non-germ cells. In the case of germ cell effects, we refer here to two types of preconception events: First, the exposure may directly alter the sperm or ova of an individual so as to induce a reduction of fertility or frank infertility. Secondly, heritable alterations may be induced in egg or sperm, and those may be transmitted at conception to the progency, with, at times, clinically detectable genetic disease in the child. Alternatively, when maternal exposure to a reproductive hazard has taken place after conception then we are dealing with somatic effects, which may result among other things, in stillbirth, prematurity, or congenital mal-

formation. The induction of somatic cell damage which leads to malformation of the embryo or fetus will be referred to here as the teratogenic effect of a physical or chemical agent, to distinguish it from the genetic effect of alterations induced in germ cells.

My thesis today will be that while germ cell effects in humans are notoriously difficult to establish, we may reasonably assume that such effects of gene-altering (i.e. mutagenic) chemicals do occur, as do those of mutagenic physical agents like ionizing and perhaps non-ionizing radiations. The problem is that we have for several reasons become considerably better at estimating somatic cell effects, such as teratogenicity and carcinogenicity, than we have at estimating true genetic effects.

The magnitude of the problems may quickly be grasped by a summary consideration of the demonstrated late effects in the Hiroshima and Nagasaki populations. In a sense, and sadly, the studies of the Hiroshima and Nagasaki A-bomb survivors have provided us with much of what we now know about the effects in humans of exposure to high, and low, single doses of a known mutagen and teratogen, namely ionizing radiation. The dose range was wide enough and the size of the exposed population was large enough so that important lessons could be learned about appropriate approaches to human populations at risk of somatic or genetic abnormalities because of exposure to a potent environmental hazard.

In essence, the major effects described to date in Japan among the A-bomb survivors are somatic effects. That is, numerous types of cancers have been shown to be increased in the survivors (breast cancer, lung cancer, thyroid cancer and leukemia, especially), and major effects have been demonstrated in those exposed in utero (namely, mental retardation and small head circumference). However, virtually all of the studies on those conceived after parental exposure to A-bomb have been negative. These studies have involved many tens of thousands of such offspring, with numerous end-points having been examined, especially by Professors James V. Neel (University of Michigan) and William J. Schull (University of Texas). The end-points included early miscarriages (spontaneous abortions), congenital malformations, the sex ratio of the progeny, and, more recently, chromosomal abnormality and genetically-determined biochemical abnormality. In these major manifestations of a possible genetic effect of the ionizing radiation, no increases were seen, suggesting that while there may have been such genetic effects induced, their magnitude in such as to render them, by current and then-current (1950's and 60's) technologies, non-detectable.

So, from Hiroshima and Nagasaki comes an important lesson: for a known physical mutagen, like ratiation, at single high doses, it is not yet feasible to demonstrate heritable genetic effects in humans. We, of course, do not know whether this lesson will apply to chemically-exposed human populations, but it seems likely that unless the agent in question is extremely genotoxic, and unless many thousands are exposed, we are likely to continue for the foreseeable future to have trouble proving that any chemical has exerted a "genetic", i.e., heritable effect in humans.

On the other hand, the post-conception somatic level reproductive studies are more likely to be useful, if properly done from an epidemiological point of view. I have mentioned above the major reproductive parameters of congenital malformation stillbirth and prematurity; but must acknowledge that these may, in fact, be either genetic or somatic, i.e., either the result of preconception of postconception exposure. To these reproductive end-points we might add numerous others, namely, neonatal deaths, decreased birthweight, childhood malignancies, etc., which again may be the result of either heritable or somatic changes.

To do these studies properly is often difficult, because, as pointed out by Stein, Warburton, et al. (in "Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards," A. D. Bloom, ed., March of Dimes, White Plains, N.Y., 1981) the exposed populations often consist of only a small number of persons; the exposure may produce only rare events such as a highly specific congenital malformation or pattern of malformations—as thalidomide did; and the exposure may be ill-defined, in terms of the agent or agents, the dose, and the duration.

Two well-known recent incidents illustrate this point. At Three Mile Island, the estimated exposure dose of persons living within 10 miles of the nuclear plant was on average not more than 2–3 mrem, a very low radiation dose, indeed. Now, we consider 2 to 4 percent of all livebirths to be associated with a congenital malformation, so that if there has been 1,000 pregnant women living within that 10 mile radius (there were in fact somewhat fewer), we would have expected a normal background rate of 20 to 40 anomalies, and even 10 or 20 percent increase would have been unlikely to be detected. Thus, even assuming that all the embryos and fetuses were equally sensitive, which they were not, since there is considerable stage-of-

pregnancy variation in radiation sensitivity, a small increase in malformations, such as at a low level of exposure, would clearly not be detectable. The exception to this would be if a highly specific pattern of malformations were frequently induced, which in itself is not likely.

At the Love Canal, the residents were found to have a wide range of chemicals, at low concentrations, in the basements of their homes. So, the situation there was multiple agent exposure, over a long period of time. But the size of the presumably at-risk population (in tôtô, 5,000 persons) would have made it very difficult, though not impossible, to obtain definitive data on, for example, congenital malformations, a parameter which is more easily confirmed and is more reliable than spontaneous abortion. For spontaneous abortion, the range of normal variation seems to be considerable from study to study, with estimates of 15 to 50 percent of all conceptuses aborting.

RECOMMENDATIONS

A. Negative studies.—I distinguish here "definitive" data from "useful" data. In much of the thinking that has gone on about mutagens in the workplace or in the general environment, there has been a certain reluctance to commit funds and manpower to study workers (and their offspring) or residents of a geographic area for evidence of reproductive effects when the expectation is that no effects will be found. As in Hiroshima and Nagasaki, the power-social, economic, political and scientific—of a negative study is not to be underestimated, especially now that we are in the relatively uncertain times of toxic waste dumps and leaky nuclear power plants.

B. Priorities in population research.—Were we to try to set population-type priorities for proper epidemiological and laboratory studies, we clearly should list as our top priority that population group which has been exposed to high doses to a powerful mutagen. Next, we might wish to study that group which has been exposed to mixtures of known, potent mutagens at unknown doses. Third, we would rank that group exposed to low doses or to weak mutagens; and lastly, that exposed to low doses to mixtures of weak mutagens (deSerres and Waters, ibid., p. 120). In other words, I suggest that we try to set priorities for proper epidemiological and laboratory studies on environmentally exposed human population, so that reliable data can be collected, in a systematic way, to inform the scientific community and the public of the nature and type of any effects seen, both long-term and short-term.

C. Newer technologies.—Newer technologies also need to be encouraged. Many methods have been developed as part of the continuing search for short-term in vitro or experimental animal test systems. More than 35 such assays have now been described, but most of them are assays of gene or chromosomal damage in somatic cells, usually nonhuman, and are not measures of true, heritable mutations passed on from one generation to the next. For inherited mutations, there are primarily mouse colony assays; but, extrapolating from mouse to man is neither simple nor satisfying. Thus, newer approaches to detection of germinal mutations in man are needed, as are newer approaches to detection, before clinical disease arises, of somatic mutations. [Identification of cancer-prone individuals would be one such approach to somatic mutation in man.]

The parameters of genetic damage discussed above (such as congential malformations and spontaneous abortion) are, really, indirect measures of an agent's effect on the genetic material. More direct measures are needed, and are, in fact, likely to become available. There are now molecular approaches to induced mutation that appear to be very promising and require support. The principles here involve isolation of DNA from cells, the "cutting up" of the DNA into management fragments, and the determination of the sequence of DNA bases in the fragments to enable investigations to figure out what alternations have taken place. Early studies have shown, for example, that specific parts of the DNA are highly sensitive ("hot spots", as defined by Haseltine and colleagues at Harvard). It is at this time unclear whether this approach will prove useful for human population monitoring, but this approach to molecular mutagenesis needs encouraging.

D. Population screening and monitoring.—The two currently extant approaches to human population studies which may be distinguished are screening and monitoring. We define monitoring in this context as the use of some parameter (such as chromosome damage) as an indicator of exposure. Screening, on the other hand, implies evaluation of the genetic constitution of the individual, as to determine whether the person has a genetic predisposition to develop medical problems under certain workplace conditions. At present, the two genetic approaches of such testing are: (1) Cytogenetic-chromosome studies looking for rearrangements or breakage of

normal chromosome stucture; and (2) Biochemical—in which specific normal parameters of metabolism are either simply variant or pathological, i.e., leading to disease. For the most part, it seems that there is litle reason to screen humans now, in terms of determining sensitivity to mutagen exposure, since none of the biochemical tests are well established as being able to do that, and only a very few cytogenetic tests are thus far promosing in this regard.

For monitoring, however, there is some reason to consider using cytogenetic tests in persons suspected of being exposed to genetically toxic chemicals or radiations. The problem is the presence of chromosomal aberrations may or may not have reproductive implications—we assume most induced genetic alterations, or mutations, to be deleterious—and there has as yet been no clear example of a person exposed to a genotoxic agent, with somatic cell damage in him or herself, and the preconception exposure provable as the cause of genetic disease in the offspring.

So, one of the major research thrusts needed, in my view, is one which will have as its goal the improved monitoring and perhaps screening of human populations for genetic effects of environmental hazards. Rather than stepping away from this thorny issue, I suggest that we need to stimulate research in the area, to improve the methods now available, and to develop new approaches. This, then, is for monitoring exposed, or putatively exposed persons or groups of persons, to see if heritable effects can be demonstrated, at reasonable levels of sensitivity. I do believe that monitoring for reproductive effects is feasible, using a combination of sensitive laboratory techniques and proper epidemiological/statistical study design.

The role of Federal and State agencies must be primary in all of this, as few local municipalities will have the expertise at hand. But, within state and federal agencies the lines of responsibility must be clear. The public's sense of well-being will be sufficient only when reasonable statements are made on behalf of well-informed officials, who are sensitive to community needs. Further, there are professional groups (such as the American Society of Human Genetics and the Environmental Mutagen Society) that can be called upon, as mixes of government and largely University-based scientists, with expertise and relative objectivity to assist communities in need, where the public's skepticism may be great about state or federal agencies.

E. Need for an environmental study group on genetic effects.—Chemical and physical agents that are mutagenic are ubiquitous in our world. Radiation scientists are concerned about genetic effects; chemically-oriented investigators who think about the public health are concerned about genetic effects; and public officials must be concerned, as you obviously are, with the genetic well-being of our species. We require a high level scientific-governmental body which will begin to formulate research strategies for long-term studies of subsets of our population which are thought to be exposed to mutagens. We need this research on many levels. We need a systematic exploration of promising laboratory approaches for the detection of mutation. These will include research on biochemical and cytogenetic studies in humans and research into basic mechanisms of induced mutation (especially at the molecular level). We need expanded research into the clinical genetic effects of environmental agents, i.e., research into ways in the which induced genetic alterations express themselves clinically. And, of course, we need much research into the epidemiological study of genetic effects. Population studies of the numerous parameters of genetic damage need greater definition and refinement than they now have. I would suggest that there is no greater responsibility than the protection of future generations from the environmental calamities of today.

Mr. Gore. Thank you very much.

Our fourth witness will be Dr. Jeanne Manson, University of Cincinnati Medical School. Dr. Manson, welcome.

Dr. MANSON. I have been conducting laboratory research on the reproductive toxicity of environmental agents in the Department of Environmental Health since 1974, and more recently in the Department of Obstetrics and Gynecology at the University of Cincinnati. I have served as a consultant to a variety of agencies in this area, and have had experience for about the last 8 years in examining the reproductive effects of environmental agents in laboratory animal studies. Today, I speak to you as a private citizen, and my testimony consists of personal opinion based upon this experience.

First, I would like to commend Congressman Gore and the subcommittee for the clarity with which the questions posed to this

panel were formulated. The fact that definitive answers cannot be given to many of these questions underlies the necessity for this hearing, and also for more intense efforts on the regulatory, industrial, and academic levels to define the impact of chemical exposure on human reproduction.

The first question posed to the panel relates to the efforts made to examine research on hazards to human reproduction and to inform the public about the potential hazards. I feel that a great deal of progress has been made in this area. I know that a number of workshop proceedings and publications have been put together over the past 5 or 6 years in which the available research information is synthesized, and the areas in which additional work is needed are laid out. I feel at this point that it is no longer productive, at least for the next span of time, to continue synthesizing the information and continue making recommendations. I think we have put a lot of effort into synthesizing what we know about chemical hazards to reproduction, a process that many people in this room have contributed to. The needs are clearly laid out.

I think that two documents that have already been mentioned—that is, the CEQ document, which takes a broad overview of the problem and includes human studies as well as laboratory animal studies; and the March of Dimes publication of which Dr. Bloom was the editor, which is mainly concerned with epidemiologic studies of exposed men and women—do an excellent job of describing what we know and laying out where we need to do additional work.

So I really feel that, at the present moment, the need is for funding and regulatory agencies to look at these documents and move from that point. There is no additional need to repeat this exercise.

The authors of the CEQ document recommend more comprehensive, uniform data collection on reproductive outcomes; further research to determine the frequency of conception failures and early spontaneous abortion; further research to establish the importance of environmental factors in reproductive impairment; more research to improve the efficiency, reliability, and sensitivity of existing screening systems for reproductive effects, in particular development of useful short-term tests; development of a reliable predictive system requiring more research in epidemiology and comparative toxicology; and more research on dose-response relationships for agents which affect reproduction in humans.

I think the second recommendation to perform further research to determine the frequency of conception failures and early spontaneous abortion is most important in terms of surveillance of human populations. One factor that has hindered progress in identifying human reproductive toxicants has been the overemphasis on birth defects as the major adverse pregnancy outcome. There are tables of data presented in the testimony showing that the frequency of birth defects per 100 ranges between 2 and 3 percent of livebirths. These are major defects that are apparent at the time of birth. The frequency of spontaneous abortion, particularly those involving chromosomal aberrations, ranges between 30 and 40 percent per 100. We know that approximately one-third of spontaneous abortions occurring between the 8th and 28th weeks of gestation contain embryos with chromosomal anomalies. Of the two-

thirds spontaneously aborted embryos that are chromosomally normal, about half have physical malformations.

Exposure or insult of embryos with toxic substances, leads to spontaneous abortions in the majority of cases. Many that are malformed abort, and very few make it through to term. So, given the rarity of chromosomal anomalies and physical malformations in liveborns, it is very unlikely that we will be able to detect the role of chemical agents on insult to embryos unless the exposed population is exceedingly large or the defect is unique and rare in livebirths.

At this juncture, there are carefully formulated documents, and well defined research which indicate that we need to shift our emphasis from livebirth outcomes to earlier outcomes of spontaneous abortion and infertility. Additional research should be conducted to ascertain the association between occupational and environmental exposures and the frequency of spontaneous abortion. We now know enough about this association to begin setting up surveillance systems at the present moment.

Another area not specifically mentioned in the CEQ document or in the March of Dimes document that I feel is important in identification of human reproductive toxicants is awareness on the part of obstetricians about the reproductive hazards of occupational exposure. While schemes for developing recommendations for the pregnant worker in terms of whether she should continue working, should have a job modification, or should not continue working have been published and widely circulated by NIOSH/ACOG, it has been my experience that obstetricians know relatively little about the reproductive toxicity of environmental and industrial chemicals, in contrast to therapeutic drugs, and have no available data source to consult for information. This situation could be remedied by inclusion of occupational health training during OBGYN residency programs. Even more important, however, would be availability of information on chemicals in data banks which could make information rapidly accessible to the physician.

A related issue is that a clearly defined process for extrapolating existing information from laboratory animals studies to exposed humans does not exist. This makes it difficult to fully utilize what information is available—and there is certainly little enough that is available—on specific chemicals to predicting the risk to exposed humans.

A typical experience I have had is to be called by a physician or an industrial hygienist inquiring about a patient or a worker, usually a pregnant female, who has been exposed to a drug or a chemical before she knew she was pregnant, and often during the critical organogenesis period. In the best of situations, the most I can do is go to the literature that I have immediately available to me, pull out laboratory animal studies on the chemical in question, and relay information to the physician. The physician then has to make difficult decisions, such as whether to recommend termination of a pregnancy, based on information that does not take into account important factors such as level of exposure, genetic susceptibility, multiplicity of exposure or length of exposure. The physician also has to make this decision very rapidly, unlike exposure to cancer where one might have a 10- or 20-year latency period for the devel-

opment of the disease. In this case, the physician usually has to make a decision about termination of a pregnancy within weeks—within the period of time, of course, when it is safe and legal to perform an induced abortion.

I think that, under these circumstances, a data bank on the reproductive toxicity of chemicals should be developed which can provide rapid access to information. Existing information derived from animals, however, will continue to be of limited usefulness unless an approach to extrapolating this information to human risk based on genetic susceptibility, level and length of exposure, and the relative toxicity of chemicals can be developed. Surely a chemical such as methylene chloride, which is proposed to have some degree of reproductive toxicity, should not be ranked at the same level as dibromochloropropane. So we need to develop some kind of a ranking system for severity of reproductive toxicity.

The committee has requested that the panel identify data and research gaps in chemical hazards to reproduction. In my opinion, the largest gap exists in ascertaining female infertility. There are tables of data presented in the testimony with lists of epidemiologic and clinical tests currently in use for measurement of female infertility. These are widely believed to be insensitive tests. The same situation also exists for laboratory animal studies. The quality of measurements in conventional protocol tests of female fertility and pregnancy outcome in rodents is considered to be low. Measures of germ cell toxicity, libido and implantation really are not very quantitative.

So a clear need exists for development of clinical test methods to ascertain human female infertility, and for development of more sensitive test methods for laboratory animals. Both clinical and laboratory methods for male fertility are far more advanced than for female fertility, most likely due to the possibility of making direct observations on germ cells in the ejaculate of the male. There are tables of data presented on conventional measures that can be made from semen samples in the testimony. One a research gap that exists in the area of male reproductive toxicity is the absence of a quantitative correlation between alterations in semen parameters and male fertility and the potential for adverse pregnancy outcome. We know that a decrease in sperm count and in elevation in the level of abnormally shaped sperm are adverse effects. But to what extent these alterations predict the infertility of the male or the potential of adverse pregnancy outcome is not known. That is clearly a research gap.

Another area identified for commentary by the panel is the mechanism for priority setting. One major distortion in this process is that regulations of occupational and environmental chemicals are usually based upon carcinogenic activity. Standards of exposure are set to protect the population from excess cancer risk. While it is true that many, if not most, reproductive toxicants also possess mutagenic and carcinogenic activity, there are numerous examples of agents that adversely affect the reproductive system at exposure levels lower than those required to induce cancer. Well known examples of this are lead, mercury, cadmium, the glycol ethers, TCDD, and a number of pesticide products. The setting of standards in these cases ultimately depends upon whether the greater

concern of society is to be protected from reproductive dysfunction or from cancer.

In terms of the last points raised by the committee, I feel that there is reasonably good coordination of Government research efforts, particularly at the bench level. Again, I am sure that many of the people in this room know each other and run into each other at meetings. I am concerned about the level of coordination at what you might consider to be the administrative level of Government agencies. As I have said, there have been a number of documents written and a number of workshops held making clearly defined recommendations about research needs in the area of reproductive toxicology and what kinds of gaps there are in our information. But at the present moment, this kind of information is not being translated into increased funding in this area or into clearly defined funding programs like requests for applications and proposals by Government agencies. I think that is really the place where we need to begin working at this time. Many of the major documents that had been written on reproductive toxicity involve joint collaborations between EPA, NIOS, NIEHS, OSA, and NTP.

I do believe that the level of funding for relevant research is inadequate, especially in comparison to the amount of funding going into cancer research. Again, I think the CEQ document outlines the major research areas adequately. The only area I would add to this document is to increase funding for development of better clinical and laboratory tests for measuring female infertility.

[The prepared statement of Dr. Manson follows:]

Statement of Jeanne M. Manson

I am Jeanne M. Manson. I have been conducting laboratory research on the reproductive toxicity of environmental agents in the Department of Environmental Health since 1974, and more recently in the Department of Obstetrics and Gynecology at the University of Cincinnati. I have served as a consultant in this area to the EPA on the Science Advisory Board, to NIEHS on the National Advisory Council, and to the Council on Environmental Quality (CEQ) as a reviewer of the document "Chemical Hazards to Human Reproduction (1). Today I speak to you as a private citizen, and my testimony consists of personal opinion based upon my experience in the field of Reproductive Toxicology over the past 8 years.

First, I would like to commend Congressman Gore and the Subcommittee on Investigations and Oversight for the clarity with which the questions posed to this panel were formulated. That definitive answers cannot be given to many of these questions underlies the necessity for this hearing, and for more intense efforts on the regulatory, industrial and academic levels to define the impact of chemical exposure on human reproduction.

The first question posed to the panel relates to efforts made to examine research on hazards to human reproduction and to inform the public about the potential hazards. I feel that progress has been made in this area, and that a number of recent documents have been prepared which address these issues. Documents I am aware of, and have participated in formulating, include the following:

1) Chemical Hazards to Human Reproduction — CEQ, 1981 (1)

2) Guidelines for Reproductive Studies in Exposed Human Populations — March of Dimes, 1982 (2)

3) Reproductive Toxicology Workshop — NIEHS, 1980 (3)

4) Work and the Health of Women, V.R. Hunt, 1979 (4)

5) Workshop on Methodology for Assessing Reproductive Hazards in the Workplace — NIOSH/SOEH, 1978

6) Guidelines on Pregnancy and Work — NIOSH/ACOG, 1977 (6)

The CEQ document, which in my opinion gives the broadest view of the area and which accurately highlights the major research problems, suggests the need for:

- more comprehensive, uniform data collection on reproductive outcomes;
- further research to determine the frequency of conception failures and early spontaneous abortion;
- further research to establish the importance of environmental factors in reproductive impairment;
- more research to improve the efficiency, reliability and sensitivity of existing screening systems for reproductive effects, in particular development of useful short-term tests;
- development of a reliable predicitive system requiring more research in epidemiology and comparative toxicology; and
- more research on dose-response relationships for agents which affect reproduction in humans.

Of these recommendations, I think the second one on further research to determine the frequency of conception failures and early spontaneous abortion is most important in terms of surveillance of human populations. One factor that has hindered progress in identifying human reproductive toxicants has been the over-emphasis on birth defects as the major adverse pregnancy outcome. As can be seen from Table 1, spontaneous abortions, particularly those involving chromosomal anomalies, are a more prevalent adverse outcome than birth defects. We now know that approximately 1/3 of spontaneous abortions occurring between 8-28 weeks of gestation contain embryos with

chromosomal anomalies. Of the 2/3 spontaneously aborted embryos that are chromosomally normal, about half have physical malformations (2). Since the frequency of chromosomal anomalies and malformations is much higher among abortions than livebirths, it is more feasible to conduct surveillance studies on abortions. Given the rarity of these outcomes in liveborns, they are likely to be missed unless the exposed population is large, or the defect is unique and rare. Thus, additional research should be conducted to ascertain the association between occupational/environmental exposure, and the frequency of spontaneous abortion. Enough is known about this association at the present time to begin setting up surveillance systems.

Another area not mentioned in the CEQ document that I feel is important in identification of human reproductive toxicants is awareness on the part of obstetricians about the reproductive hazards of occupational exposure. While schemes for developing recommendations for the pregnant worker in terms of whether she should continue working, should have a job modification or should not continue working have been devised by NIOSH/ACOG (6), it has been my experience that obstetricians know relatively little about the reproductive toxicity of industrial chemicals (in contrast to therapeutic drugs), and have no data source to consult for information. This situation could be remedied by inclusion of occupational health training in residency programs. Even more important, however, is the availability of data banks on chemicals which could make information rapidly accessible to the physician.

A related issue is that a clearly defined process for extrapolating existing information from laboratory animal studies to exposed humans does not exist. This makes it difficult to fully utilize what information is available on specific chemicals to predicting the risk to exposed humans. A typical situation I have encountered is that a

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physician will call me inquiring about a pregnant woman who has been exposed to a chemical or drug before she knew she was pregnant, often during the critical organogenesis period. In optimal situations the best information I can offer are results of laboratory animal studies in which the particular agent was administered under controlled conditions at exposure levels far exceeding those likely to have been encountered by the patient. The physician is then in the position of having to make difficult decisions, such as whether to recommend termination of the pregnancy based on information that does not take into account factors such as level of exposure, genetic susceptibility, multiple exposures, or length of exposure. These decisions usually also need to be made quickly, before the pregnancy continues beyond the period of time when it is safe or legal to perform an induced abortion. Under these circumstances, a data bank on the reproductive toxicity of chemicals should be developed which can provide rapid access to information. Existing information derived from animal studies, however, will continue to be of limited usefulness unless an approach to extrapolating this information to human risk based on genetic susceptibility, level and length of exposure, and relative toxicity of chemicals can be developed.

The committee has requested that the panel identify data and research gaps in chemical hazards to reproduction. In my opinion, the largest gap exists in ascertaining female infertility. Table 2 contains a list of epidemiologic and clinical tests currently in use for measurement of female infertility. These are widely believed to be insensitive. The same situation exists for laboratory animal studies. Table 3 contains a description of the quality of measurements in conventional protocol tests of female fertility and pregnancy outcome in rodents. Measures of germ cell toxicity, libido and implantation are relatively weak. A clear need exists for development of clinical test methods to ascertain human female infertility, and for development of more sensitive test methods

for laboratory animals. Both clinical and laboratory methods for male fertility are more advanced than for female fertility, mostly due to the possibility of making direct observations on germ cells in the ejaculate. Conventional measures that can be made on semen samples are listed in Table 4. A research gap that exists in the area of male reproductive toxicity is development of a quantitative correlation between alterations in semen parameters to male fertility and the potential for adverse pregnancy outcome. For example, decrease in sperm count and elevation in the level of abnormally shaped sperm are considered adverse effects, but to what extent these alterations predict infertility and adverse pregnancy outcome is unknown.

Another area identified for commentary by the panel is the mechanism for priority setting. One major distortion in this process, in my opinion, is that regulations of occupational and environmental chemicals are usually based upon carcinogenic activity. Standards of exposure are set to protect the population from excess risk to cancer. While it is true that many, if not most, reproductive toxicants also possess mutagenic and carcinogenic activity, there are numerous examples of agents that adversely affect the reproductive system at exposure levels lower than those required to induce cancer. Examples of this are lead, mercury, cadmium, the glycol ethers, TCDD and Nitrofen. The setting of standards in these cases ultimately depends upon whether the greater concern of society is to be protected from reproductive dysfunction or from cancer.

In terms of the last points raised by the committee, I feel that there is reasonably good coordination of government research efforts. Most of the major documents listed at the beginning of this presentation involved joint collaborations between EPA, NIOSH, NIEHS, OSHA, and NTP. Finally, I believe that the level of funding for relevant research is inadequate, especially in comparison to the amount of funding going into cancer

research. I believe the CEQ document outlines the major research areas which need to be developed by increased funding. The only area I would add is increased funding for development of better clinical and laboratory tests for measuring female infertility.

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1. Chemical Hazards to Human Reproduction, Council on Environmental Quality, January 1981.

2. Report of Panel II: Guidelines for reproductive studies in exposed human populations, In Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards, Bloom, A.D., ed., March of Dimes Birth Defects Foundation, 1981, pp 37-110.

4. Hunt, V.R. Work and the Health of Women, CRC Press, Boca Raton, Florida, 1979.

5. Infante, P.F., and Legator, M. Workshop on methodology for assessing reproductive hazards in the workplace: Recommendations for future research. Env. Res. 20(1979):217-223.

6. Guidelines on Pregnancy and Work, The American College of Obstetricians and Gynecologists, NIOSH Publication No. 78-118, 1977.

TABLE 1

FREQUENCY OF SELECTED REPRODUCTIVE ENDPOINTS

EVENT	FREQUENCY PER 100	UNIT
Failure to conceive after 1 year	10-15	Couples
Spontaneous abortion 8-28 weeks	10-20	Pregnancies or Women
Chromosomal Anomalies in spontaneous abortions, 8-28 weeks	30-40	Spontaneous Abortion
Chromosomal anomalies from amniocentesis, 35 years	2	Amniocentesis Specimens
Stillbirths	2-4	Stillbirths and Livebirths
Brithweight 2500	7	Livebirths
Birth defects	2-3	Livebirths
Chromosomal anomalies, livebirths	0.2	Livebirths
Severe mental retardation	0.4	Children to age 15 years

(Report of Panel II, 1981)

TABLE 2

FEMALE INFERTILITY

EPIDEMIOLOGIC METHODS

1. LIFE-TABLE RECORD ON ALL PREGNANCIES AS THEY OCCUR
2. STANDARD FERTILITY INDEX, ACTUAL NUMBER OF LIVE CHILDREN CONCEIVED COMPARED TO EXPECTED NUMBER OF BIRTHS (NATIONAL FERTILITY SURVEY)

CLINICAL METHODS

1. HORMONE EVALUATION
2. VAGINAL CYTOLOGY

TABLE 3

PARAMETER	QUALITY OF MEASUREMENTS
1) Effect on germ cells	very poor
2) Gametogenesis	poor
3) Libido	poor
4) Fertilization	good
5) Implantation	poor
6) Embryonic growth and survival	not measured
7) Fetal growth and survival	good
8) Neonatal growth and survival	good
9) Lactation	fair
10) Post-weaning growth and maturity	good

TABLE 4

SEMEN ANALYSIS

1. GROSS PARAMETERS
   - A. EJACULATE VOLUME
   - B. SPERM CONCENTRATION
   - C. PERCENTAGE MOTILE CELLS
   - D. SPERM MORPHOLOGY

2. FUNCTIONAL PARAMETERS
   - A. SPERM MOVEMENT CHARACTERISTICS
   - B. SPERM-CERVICAL MUCUS INTERACTIONS
   - C. SPERM-OOCYTE INTERACTIONS

3. GENETIC PARAMETERS
   - A. YFF TEST

4. SEMINAL FLUID CONSTITUENTS

CURRICULUM VITAE

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EDUCATION:

B.A.	Emmanuel College, Boston, Massachusetts	1965-1969
Ph.D:	Ohio State University, Columbus, Ohio Developmental Biology	1969-1974
Fellowship:	University of Cincinnati, College of Medicine Department of Environmental Health Environmental Teratology Postdoctoral Fellow	1974-1976

PROFESSIONAL APPOINTMENTS:

Assistant Professor of Environmental Health University of Cincinnati, College of Medicine	1976-1980
Associate Professor of Environmental Health University of Cincinnati College of Medicine	1980-1982
Associate Professor of Obstetrics and Gynecology University of Cincinnati College of Medicine	1982-Present

UNIVERSITY ACTIVITIES AND APPOINTMENTS:

Search committee member for Chairman of Obstetrics and Gynecology Department	Spring, 1981
Chair of Instrument Committee, Department of Environmental Health	1979-1982
Program Coordinator, Reproductive Biology Group Department of Environmental Health	1980-1982

PROFESSIONAL ACTIVITIES:

Science Advisory Board, Health Effects Panel, EPA	1978-1980
National Advisory Environmental Health Sciences Council, N.I.H.	1979-1982
Marine and Freshwater Biomedical Center Grant Program, N.I.E.H.S. Site visits and study section meetings	1978
Science Review Panel for Health Research, E.P.A. Study section for review of E.P.A. grants	1981-Present
Associate Editor, Teratogenesis, Carcinogenesis and Mutagenesis	1979-Present
Editorial Board, Toxicology and Applied Pharmacology,	1981-Present
Evaluation of Current Environmental Research and Establishment of Priorities, E.P.A.: Chair of the Teratogenic and Reproductive Effects Group	4/24-25, 1979
N.I.H. Consensus Development Conference, "Defined Diets and Childhood Hyperactivity", panel member	1/12-15, 1982

ORGANIZATIONAL MEMBERSHIPS:

Developmental Biology
Teratology Society
Society of Toxicology
Environmental Mutagen Society

GRADUATE TEACHING EXPERIENCE:

Reproductive Toxicology. Lectures and discussions covering the roles played by mutagens, carcinogens and teratogens on the reproductive process. Chemical insult during oogenesis, spermatogenesis and early, middle and later periods of development will be emphasized. Three graduate credits, primary instructor and director.

Teratology I - Principles. This course explores the principles, causes and mechanisms of abnormal development. The clinical problems of birth defects are considered along with methods of animal testing for potential environmental teratogens. Three graduate credits, five lectures.

Toxicology I. Entry, action and elimination of toxic chemicals, dose-response relationship: experimental toxicology, design, interpretation and application of data. Three graduate credits, four lectures.

Toxicology II. Organs and systems as routes of entry and elimination of poisons; nature of toxic responses of toxic organs. Four graduate credits, six lectures.

ADVISEES:

Postdoctoral:

Dr. Julia George: Role of 3-methylcholanthrene metabolism in transplacental carcinogenesis. 1981 - Present

Doctoral:

Dr. Logan Stone: "The effects of TOK (2,4-dichlorophenyl-p-nitrophenyl ether) on lung maturation". Graduated Fall, 1978

Dr. Richard Costlow: "Investigation of the target organs in nitrogen-induced neonatal death after in utero exposure". Graduated Spring, 1982

Mr. Raymond York, Ph.D. candidate: "Transplacental carcinogenesis associated with genetic differences at the Ah locus". Anticipated graduation, Fall of 1982

Mr. Brian Hardin, Ph.D. candidate: "Disposition and teratogenicity of methylene chloride". Anticipated graduation, Spring of 1983.

Masters:

Mr. Steven Henne: "Neurotoxic effects of chronic manganese intoxication". Graduated Spring, 1979

GRANTS AND COOPERATIVE AGREEMENTS:

Postdoctoral Fellowship, N.I.H. #GM02660, 1974 - 1976

Principal Investigator, "Influence on thalidomide on limb regeneration", Basic Research Science Grant, University of Cincinnati College of Medicine, 1976 - 1977, $2000

Principal Investigator, "In vitro teratologic assay with P-450 metabolism", NIH-CHD #10868, April 1, 1977 - 1980, $123,493.

Principal Investigator, "Teratogenicity of chlorinated hydrocarbon solvents", NIH-ES #01601, August 1, 1977 - 1980, $166,501

Principal Investigator, "Herbicide-induced respiratory distress in neonates", NIH-CHD #13299, August 1, 1979 - 1982, $217,878

Principal Investigator, "Correlation between placental metabolism of polycyclic aromatic hydrocarbons and fetal insult", Ohio Coal Research Laboratory Association, August 8, 1980 - February 1982, $40,000

Principal Investigator, "Cell death and somatic mutation in teratogenesis", EPA Grant #807774010, October 14, 1980 - 1983, $333,639

Principal Investigator, "Reproductive/teratologic assessment and pharmacokinetics of selected organochlorine contaminants in drinking water", Cooperative Agreement, EPA 1981 - 1984, 1st year, $102,448

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Bornschein, R., Hastings, L. and Manson, J.M. 1980. Behavioral toxicity in the offspring of rats following maternal exposure to dichloromethane. Toxicology and Applied Pharmacology 52, 29-37.

Stone, L.C. and Manson, J.M. 1981. Effects of the herbicide 2,4-dichlorophenyl-p-nitrophenyl ether (Nitrofen) on fetal lung development in rats. Toxicology 20, 195-207.

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Manson, J.M. and Bazzoli, A. Influence of thalidomide on salamander forelimb regeneration. Midwest Regional Developmental Biology Conference, Hueston Woods, Ohio, April, 1976.

Manson, J.M. and Smith, C.C. Effects of the teratogen cytosine arabinoside on the in vivo and in vitro development of embryonic mouse limbs. Tissue Culture Association Meetings, Philadelphia, Pennsylvania, June, 1976.

Manson, J.M. and Simons, R. In vitro teratogenic assay system with P-450 metabolism. Teratology Meeting, Reston, VA, May, 1977.

Stone L. and Manson, J.M. The effect of TOK on lung maturation in the rat fetus. ASPET Meetings, Columbus, Ohio, August, 1977.

Bazzoli, A.S., Scott, W.J., Manson, J.M. and Wilson, J.G. Thalidomide induced limb malformations during the nerve dependent stage of newt forelimb regeneration. Fifth International Conference on Birth Defect, Montreal, Quebec, August, 1977.

Manson, J.M. Reproductive hazards in the workplace: Inadequacy of current testing methods. Conference on Protective Legislation and Women's Employment, Smith College, Northampton, Mass., November, 1977.

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Manson, J.M. Presentation of talk, "Limb bud culture," in Consensus Workshop on In Vitro Teratogenesis Testing, Arkadelphia, Arkansas, NCTR-EPA, August 2-5, 1981.

Manson, J.M. Lectures on teratogenicity in the Latin American Course on Genetic Toxicology, Mexico City, Mexico, August 24-28, 1981.

Manson, J.M. Cell death and somatic mutation in teratogenesis. Seminar at Oak Ridge National Laboraty, Mammalian Genetics and Teratology Division. November 4, 1981.

Manson, J.M. Nitrofen-induced teratogenicity in the rat. Seminar at Argonne National Laboratory, Biology Division, Argonne, IL, November 19, 1981.

Manson, J.M. Role of DNA damage and repair in induction of birth defects. Brookhaven National Laboratory, Biomedical Division, Brookhaven, NY, February 3, 1982.

Manson, J.M. Teratogenicity of the herbicide, Nitrofen, in rats and potential extrapolation to humans. Johns Hopkins University Department of Environmental Health Sciences, February 18, 1982.

York, R.G. and Manson, J.M. Transplacental toxicity associated with genetic differences at the murine Ah locus. Society of Toxicology Meeting, Boston, MA, February, 1982.

George, J.D., Manson, J.M., Vater, S. and Warshawsky, D. In vivo metabolism of 3-methylchlanthrene in pregnant C57Bl/6J and DBA/2 mice. Society of Toxicology Meeting, Boston, MA, February, 1982.

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York, R.G. and Manson, J.M. The murine Ah locus: Genetic differences in toxic and tumorigenic response to transplacental exposure to 3-methylcholanthrene. ASPET/SOT, Louisville, KY, August, 1982.

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Mr. GORE. Thank you very much.

Our final witness on this panel is Dr. Vasilios Frankos, associate director of the life sciences division at Clement Associates. Dr. Frankos, welcome, and please proceed.

Dr. FRANKOS. Mr. Chairman, it is my privilege to appear here today, and I appreciate the opportunity to share with you my views on evaluation of reproductive toxicity data.

I appear here today as an individual, and my views are not necessarily those of Clement Associates, a consulting firm that specializes in risk assessment and my present employer. Nor are they the views of my former employer, the U.S. Food and Drug Administration, or of the Interagency Regulatory Liaison Group when I was Chairman of the Reproductive Toxicity Risk Assessment Task Group. I speak today out of long experience in efforts to develop scientifically defensible criteria for use by regulatory agencies in the evaluation of reproductive hazards. I was extensively involved in these efforts until March 1982 when I left Government service. As a scientist and a consultant to government, industry, and public interest groups, I have a strong professional interest in the continued development of such explicit evaluation criteria.

A fundamental assumption in the estimation of human health risks posed by chemicals is that animal toxicology test results can predict human response. This assumption is the cornerstone of most regulatory decisions regarding the safety of substances in the food supply, in drugs, and in the environment. In accepting this assumption, however, one does not assume that responses in animal models reflect exactly what will occur quantitatively or qualitatively in humans.

What is assumed is that well designed and conducted animal studies provide an indication of potential hazard to humans. Only after careful analysis of experimental results from multiple species can a degree of confidence be ascribed to the probability that this potential hazard will or will not pose a risk to the human population. If it can be demonstrated scientifically that a result from a particular animal study is not relevant as a predictor of human risk, that result would probably not be employed in making safety assessments.

In the past several years, it has become obvious to regulatory toxicologists that studies of the reproductive effects of chemicals are particularly difficult to evaluate and utilize for safety assessments. The ability of animal test species to respond to human teratogens—chemicals that cause birth defects—has been well established. Little has been published on correlation between human and animal responses for other reproductive toxicities, although the CEQ document is a good first step. All of the compounds identified as known or suspect human teratogens, except one which has not been adequately tested, have been found positive in one or more animal test species. It is reasonable, therefore, to conclude that positive teratology studies are suggestive of potential human response, and well-conducted animal studies that show reproductive effects are sufficient to raise substantial questions about the potential risk to humans.

However, interspecies variability in sensitivity to the same agent has made it difficult to decide how much animal evidence is needed

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to identify a compound as a potential human reproductive or developmental hazard. At this time, no single test species can be said to predict accurately the likely human response to a given chemical. Tests in multiple species may increase the predictive reliability of animal test data, but specific differences between the test species and the human system must be considered in evaluating the relevance of particular tests to humans. Criteria for evaluation of strength of the evidence are badly needed.

It was in this atmosphere and with the support of the FDA that, in late 1979, I proposed to the Interagency Regulatory Liaison Group that a task group be established in order to develop criteria to support consistent interpretation and use to teratologic and reproduction data by safety assessment scientists throughout the Federal Government.

Specifically, it was requested that a top-level IRLG work group be formed which would establish: one, evidence required to identify a chemical as a probably human teratogen or reproductive hazard; two, criteria for evaluating evidence for compound-induced reproductive toxicity in specific animal test systems; three, criteria for identifying a chemical as a human reproductive risks from studies in human populations; and, lastly, guidelines for estimating risks associated with various levels of exposure to a reproductive toxicant.

This request was favorably received and identified as an endeavor of interest to all the regulatory agencies and worthy of interagency interaction. FDA was given the lead on this project, and I was appointed Chairman of the IRLG Reproductive Toxicity Risk Assessment Group early in 1980. Representatives from EPA, Department of Agriculture, CPSC, FDA, NCTR, OSHA, and NIOSH served on the task group. Early in our deliberations, it became evident that each of our agencies was faced with similar problems of evaluation and interpretation of data and that communication at an interagency level was enlightening and beneficial in and of itself. Much of the first 6 months was spent learning about each agency and producing an outline of the approach we would use.

Because the field of reproductive toxicity assessment is fairly young, little rigorous review and abstraction of the current literature had been undertaken. In order to critically answer questions of threshold, predictability and sensitivity for reproductive toxicants, a compilation, abstraction and summary of the literature was needed. The task group initiated a comprehensive data extraction projects at the Oak Ridge National Laboratory's Environmental Teratology Information Center. The purpose of this was to allow better use and interpretation of existing teratology data by providing computer-compatible data review formats for accessing the reproductive toxicity literature.

It was decided early in our deliberations that before proceeding to write a specific document, we would solicit outside comments on our work plan. A work plan outline was published for comment September 25, 1980, and was well received. Most comments were favorable to the objections of the work group, but many individuals and associations requested us to approach this topic slowly, deal with science issues and not policy questions, and consult academia and industry early in the writing process. After considering this

advice, and recognizing the need for a definitive evaluation of the assumptions implicit in reproductive toxicity safety assessment, the task group decided to convene a workshop on reproductive toxicity risk assessment, which was held September 21–23, 1981.

In preparation for this workshop, the task group developed a detailed list of questions, devoid of agency policy issues, that were considered pivotal to the development of scientifically defensible criteria. These questions were worded to challenge the experts to critically examine the scientific assumptions that form the underpinnings of data evaluation and extrapolation. The questions are listed in the appendix and will not be presented. To assure balanced discussion of these questions, an attempt was made to invite a diverse cross-section of the scientific community. Six small panels of experts were selected, and every effort was made to include academia, industry and government scientists on each panel.

The workshop was well attended and provided a valuable forum for the expression of diverse scientific opinions. The small work panel environment encouraged thoughtful discussion and produced concrete answers to the difficult questions presented. This type of information had never been collected before and provided unique interdisciplinary insight into the science of reproductive toxicity data evaluation and risk assessment. After the meeting, each panel chairman was left the responsibility to produce a document that reflected the consensus of the participants. These documents would then serve as the scientific base from which the IRLG Task Group would draft specific criteria.

However, within one week of the workshop, word came that IRLG had been disbanded, and that a new group would continue the interagency communication through the President's Office of Science and Technology. We were informed that all IRLG projects were to be terminated immediately, and that no further meetings were to be held or documents completed. This ended my interagency involvement in the attempt to develop these criteria, although my personal commitment to this effort continues.

In conclusion, the information developed by the IRLG Reproductive Toxicity Risk Assessment Task Group provides unique scientific consensus data which should be used to continue the effort to draft criteria for the evaluation of reproductive toxicity data and the estimation of human risk.

The Oak Ridge reproductive toxicity computer data file, established by the IRLG provides the government and industry an opportunity to develop a central, peer reviewed, computer searchable data file for all future and past animal and human studies in reproductive toxicity. Such a file could assure more consistent evaluation of data and provide answers to many of the questions raised in my presentation. Government funding of this effort is encouraged.

In order to translate regulatory scientific dilemmas into testable research initiatives, communication among scientists from academia, industry and regulatory agencies is imperative. The use of the workshop forum is very effective and should be pursued at an interagency level.

Last, interagency communication among safety assessment scientists should be supported in a formal way because it helps identify

common problems in the application of evaluation criteria and focuses questions for future workshops on those issues which are most pertinent to the review scientists.

Thank you.

[The prepared statement of Dr. Frankos follows:]

TESTIMONY OF VASILIOS H. FRANKOS, PH. D.

Mr. Chairman and Members of the Subcommittee:

It is my privilege to appear here today and I appreciate the opportunity to share with you my views on evaluation of reproductive toxicity data. I appear here today as an individual, and my views are not necessarily those of Clement Associates, a consulting firm that specializes in risk assessment and my present employer. Nor are they the views of my former employer, the U.S. Food and Drug Administration, or of the Interagency Regulatory Liaison Group when I was chairman of the Reproductive Toxicity Risk Assessment Task Group. I speak today out of long experience in efforts to develop scientifically defensible criteria for use by regulatory agencies in the evaluation of reproductive hazards. I was extensively involved in these efforts until March 1982 when I left government service. As a scientist and a consultant to government, industry, and public interest groups, I have a strong professional interest in the continued development of such explicit evaluation criteria.

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a potential human reproductive or developmental hazard. At this time, no single test species can be said to predict accurately the likely human response to a given chemical. Tests in multiple species may increase the predictive reliability of animal test data, but specific differences between the test species and the human system must be considered in evaluating the relevance of particular tests to humans. Criteria for evaluation of strength of the evidence are badly needed.

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- o evidence required to identify a chemical as a probable human teratogen or reproductive hazard;
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but many individuals and associations requested us to approach this topic slowly, deal with science issues and not policy questions, and consult academia and industry early in the writing process. After considering this advice, and recognizing the need for a definitive evaluation of the assumptions implicit in reproductive toxicity safety assessment, the task group decided to convene a workshop on reproductive toxicity risk assessment, which was held September 21-23, 1981.

In preparation for this workshop the task group developed a detailed list of questions, devoid of agency policy issues, that were considered pivotal to the development of a scientifically defensible criteria. These questions were worded to challenge the experts to critically examine the scientific assumptions that form the underpinnings of data evaluation and extrapolation. The questions are listed in the appendix and will not be presented. To assure balanced discussion of these questions, an attempt was made to invite a diverse cross section of the scientific community. Six small panels of experts were selected and every effort was made to include academia, industry, and government scientists on each panel.

The workshop was well attended and provided a valuable forum for the expression of diverse scientific opinions. The small work panel environment encouraged thoughtful discussion and produced concrete answers to the difficult questions presented. This type of information had never been collected before and provide unique interdisciplinary insight into the

science of reproductive toxicity data evaluation and risk assessment. After the meeting, each panel chairman was left the responsibility to produce a document that reflected the consensus of the participants. These documents would then served as the scientific base from which the IRLG Task Group would draft specific criteria.

However, within one week of the workshop, word came that IRLG had been disbanded and that a new group would continue the interagency communication through the President's Office of Science and Technology. We were told all IRLG projects were to be terminated immediately and that no further meetings were to be held or documents completed. This ended my interagency involvement in the attempt to develop these criteria, although my personal commitment to this effort continues.

In conclusion:

(1) The information developed by the IRLG Reproductive Toxicity Risk Assessment Task Group provides unique scientific consensus data which should be used to continue the effort to draft criteria for the evaluation of reproductive toxicity data and the estimation of human risk.

(2) The Oak Ridge (ETIC) Reproductive Toxicity Computer data file, established by the IRLG, provides the government and industry and opportunity to develop a central, peer reviewed, computer searchable data file for all future and past animal and human studies in reproductive toxicitiy. Such a file could

assure more consistent evaluation of data and provide answers to many of the questions raised in my presentation. Government funding of this effort is encouraged.

(3) In order to translate regulatory scientific dilemmas into testable research initiatives, communication among scientists from academia, industry, and regulatory agencies is imperative. The use of the workshop forum is very effective and should be pursued at an interagency level.

(4) Last, interagency communication among safety assessment scientists should be supported in a formal way because it helps identify common problems in the applcation of evaluation criteria and focus questions for future workshops to those most pertinent to the review scientists.

APPENDIX

DATA EVALUATION AND EXTRAPOLATION QUESTIONS

1. What animal and human endpoints are useful for human reproductive risk assessment?

   a. How much should the endpoints produced by teratogens in animals be expected to mimic the human effects? How comparable are endpoints in animals and humans?

   b. Are various endpoints in developmental toxicity (e.g., fetal death, growth retardation, malformations, functional impairment) a continuum of responses or separable? What is the basis for concluding one or the other?

   c. What is the significance of transient effects (e.g., transient growth retardation or hyperactivity)?

   d. What is the relationship between maternal toxicity and fetal toxicity? Should fetal effects that occur at maternal toxic doses (especially for chemicals currently in the environment) be ignored?

   e. How should increases in spontaneously occurring defects be interpreted? How should variations (e.g., skeletal) be interpreted?

   f. What endpoints should be evaluated in animals postnatally? Should lifespan studies be included in teratology studies?

   g. What endpoints are sensitive for assessing effects on fertility and reproduction?

   h. What representative toxicity endpoints can be monitored adequately in epidemiology studies? How many cases would be needed to detect a change in each of these endpoints?

2. What evidence can be gained from pharmacokinetic studies and how can it be used for estimating potential risk to the fetus, gametes or parents?

   a. Can pharmacokinetics assist in the choice of the most appropriate test animal species, based on similarities in absorption, excretion, metabolism, placental transfer, etc.? Can dissimilarities be qualified to an extent that would make data collected in a "less-appropriate" species useful for estimating potential risks?

b. Can pharmacokinetics help establish a dosing regimen in a test system that will approximate the effective dose of a compound to which the human fetus is exposed?

c. Can pharmacokinetics define the similarities and differences in fetal exposure relative to differences in critical (sensitive) periods in development of test animals and humans?

d. What should be defined as the endpoint for evaluation (target of exposure), e.g., the conceptus, whole embryo/fetus, embryo/fetal blood, specific organ/tissues? Are embryo/fetal values any more predictive than maternal values alone?

e. Can pharmacokinetics assist in predicting thresholds?

3. How can information on mechanisms be used for interpretation of experimental data and risk assessment?

a. What can be considered an appropriate definition (not examples) of "mechanisms of action," especially as it relates to reproductive/developmental toxicity? (Maybe a definition should be stated just to use as a starting point.)

b. What information on mechanisms of action can help to explain qualitative or quantitative interspecies variation in response to reproductive toxins?

c. What information on mechanisms of action will allow the development of more appropriate models for extrapolation of animal data to humans?

d. What information on gene/toxicant interaction can be used for predicting risk? What markers of susceptibility to toxicants might be used for predicting risk?

e. What early indicators of toxicant effect might be used for predicting risk?

4. What procedures can be used for qualitative and/or quantitative risk assessment of potential human reproductive hazards using available evidence?

a. What statistical techniques, if any, are optimal for the analysis of teratology and reproduction data?

b. How do you handle the simultaneous inference problem when experiments consist of multiple doses, multiple endpoints, and multiple generations?

c. What qualitative factors contribute to identifying a compound as a potential reproductive hazard, i.e.

(1) internal consistency
(2) reproducibility in multiple species
(3) evidence of a dose response relationship
(4) molecular structure
(5) lack of overt toxicity?

d. What mathematical models can be identified for high to low dose extrapolation of both threshold and non-threshold response data?

e. What are the pros and cons of using qualitative safety factors and what factors should be used for each type of endpoint?

Mr. GORE. Thank you very much.

Thanks to all members of this panel. It has been excellent testimony.

I have a number of questions. Dr. Bloom, would you pick any one scientific research area where emphasis should be placed in order to quickly advance the state of the art of the science in the area of impairments to human reproduction?

Dr. BLOOM. I would say the general area which would, in my view, have the most direct impact in this problem of hazards to human reproduction would be the emerging field of genetic epidemiology. This would be defined generally as an area in which people interested in population-type studies come together to formalize their approach to the reproductive end point and to include in those endpoints genetic causes of abnormalities in reproduction.

I think that there are, for example, no graduate programs that I know of—there may be one or two now in genetic epidemiology in the country. But there are beginning to emerge programs to train people interested in public health and epidemiology and biostatistics and preventive medicine in the emerging discipline, which really brings together both the epidemiological population-type approach and the fundamental principles of human genetics.

Mr. GORE. Dr. Manson, you had a specific recommendation for epidemiology, and that is focusing on spontaneous abortions more than we currently do. I take it your reasoning is that since there are so many more spontaneous abortions where some sort of genetic abnormality is involved, then there are live births with the genetic abnormality, you are more likely to get better data by focusing on it.

I have always been told that there is some natural mechanism that will often produce a spontaneous abortion if there is a genetic abnormality; is that folklore, or is it accurate folklore?

Ds. MANSON. I would refer that question to Dr. Bloom, because he is the editor of the book that covered that.

Dr. BLOOM. I think that there is a fairly significant proportion of all conceptuses that will spontaneously abort, and many of those, at least a third, are thought to be at least of the early spontaneous abortions.

Mr. GORE. Did you say conceptuses?

Dr. BLOOM. Conceptuses, or conceptions, if you will.

So about a third of all of those that will spontaneously abort will have a genetic cause for the abortion. The problem with spontaneous abortion, as I see it, is that as an end point, there is so much variability that has been described in the studies that have been reported on the normal background frequency of spontaneous abortion in the human population, so that one does get estimates that range anywhere from 15 percent of all conceptuses abort to 50, 60, or even higher percentages that abort.

The problem, of course, is that many of those conceptuses will abort before the pregnant female is even aware that she is pregnant. One issue that comes up in assessing and trying to assess spontaneous abortion is that many of the spontaneous abortuses are normally lost, and that probably represents a very sizable impact on genetic factors that are not now being detected because we can't.

Dr. MANSON. I would just like to add that I agree completely with what Dr. Bloom has said about the variability of the background rate of spontaneous abortion. I also believe that that may well be a reflection of the different environmental exposures in different regions of the country. It is clear that many chromosomal aberration syndromes, if present in an embryo, simply will not permit survival to term. So you see high levels of these particular aberration syndromes in abortuses, and rarely see them in a live birth. They are incompatible with survival.

The point here is that we should all continue looking for malformations in newborns. In many ways, they probably are the type of reproductive dysfunctions that cost us the most as individuals and as a society. They are very tragic. It is unlikely we are going to be able to find environmental agents that are truly reproductive toxicants by looking at malformations alone, however we have to look at the more common outcomes such as spontaneous abortions. It is more likely that is where the damage is expressed. Embryos insulted by chemicals usually abort. In addition to looking at chromosomal aberrations, we should also take a much harder look at actual physical malformations in abortuses. There hasn't been as much effort on that level. Our chances of identifying human reproductive toxicants would be better.

Another aspect of this is that early spontaneous abortions are often confused and often looked at as female infertility. Usually a woman who aborts early is considered infertile, even though, in fact, conception has occurred. So this is perhaps, in another way of looking at it, the most common form of expression of female infertility.

Mr. GORE. The point I am getting at is a relatively simple one, I think. What you are saying is we overemphasize the amount of attention paid to abnormalities with livebirths if we just look at it from the point of view of useful data that can be gleaned from that category, because you are going to get 10 times as much useful data of that kind if you also examine abnormalities in fetuses that are spontaneously aborted; is that a fair summation?

Dr. MANSON. Yes, it is.

Mr. GORE. All right.

Dr. Hunt, since the area of human reproduction is so broad and since impairments to these processes are so numerous, how can scientists best reach a consensus on the issues of experimental protocol, research direction, interpretation of results, and so forth, all of which are necessary for the promulgation of any sound regulations or any other efforts to mitigate the undesired outcomes?

Dr. HUNT. I think you are flying in the face of reality, that that is not what happens in science. As you are aware, the funding process from the Federal Government, which is the main source, is a competitive process which we place great value on, that the best research proposals will be the ones funded. It means that you cannot necessarily rely on the short term on the pieces in the jigsaw puzzle fitting together.

It is for this reason that I spoke of the longer term, that indeed an equilibrium eventually arises, whereby the balance gets redressed if it is out of whack. I think that is the point I was trying

to make with my testimony, that we are a bit out of balance at the moment.

We have in the case of reproductive research—and I think it speaks to the previous question—that it was much less expensive to carry out descriptive epidemiology studies of adverse reproductive outcome in terms of congenital anomolies and stillbirths. That was all that could be afforded given the kind of research that was devoted to reproductive research. We are talking in terms of this rebalancing of a very important area of complex research in genetic screening, the reasons for early reproductive loss, very intense research proceedings which have been the order of the day in other areas of research—but we have operated on a shoestring for a long time, and it is incredible that we have as much as we have to present to you today.

Mr. GORE. Dr. Nisbet, let me go back to the first question that I asked you when I interrupted your statement. You say that the proportion of reproductive attempts that fail or are impaired range from 30 percent to as high as 80 percent. Can you precisely define what that figure represents again? Is that the percentage of failed reproductive attempts measured from the number of instances of sexual intercourse? Is that what you are saying.

Dr. NISBET. It was intended to represent the proportion of events of intercourse that could have led to conception, which actually do lead to a healthy livebirth. That is, includes all occasions of intercourse during the woman's fertile period where there is no specific attempt to prevent conception.

Mr. GORE. I see.

Dr. NISBET. The reasons for the failure range all the way from lack of fertility of the male or female to failure of conception to failure of development, or implantation of the conceptus to failure of the woman to carry the pregnancy to term.

Mr. GORE. How is someone supposed to react to that figure? Is that supposed to be shockingly high? I just don't know how to react to it.

Dr. NISBET. That figure is an average for the entire U.S. population, and it is an average over a substantial fraction of couples who are fully fertile, and very frequently embarrassing fertile; to the other end of the spectrum, a large number of couples, I believe it is about 7 million married couples, who are functionally infertile for one reason or another. In between, there are various ranges of partial fertility.

Whether one treats these unprotected events of intercourse as deliberate attempts to produce a child or not, the facts are that at least 30 percent are unsuccessful. If one includes the large but very uncertain number of very early failures, the fraction probably ranges up to 50, 60, 70 or, according to one estimate, 80 percent of failures. We describe that as a pervasive public health problem. If we understood the reasons for those failures, then we could at least help the couples who are unable to conceive and produce health live offspring as frequently as they would like.

Mr. GORE. We don't really know the natural baseline level, do we?

Dr. NISBET. In a sense, that is the natural baseline. We don't know to what extent that is effective by artificial factors in our environment.

Mr. GORE. OK. Do any of the other members of the panel want to help me with that?

Dr. MANSON. He really knows more about this than I do. Dr. Nisbet is, I know, referring to a paper that is widely accepted by Schlesselman, where the incidents of conceptional failures are estimated to be as high as 70 percent. That is a paper published in a peer-reviewed journal, and it widely read and accepted. Many people are very interested in that finding, and many are trying to replicate it. More conservative estimates of spontaneous abortion between 8 and 28 weeks of age range between 10 and 20 percent of live births. This underlines the point that there is a fluctuating background of infertility and early spontaneous abortion.

Mr. GORE. OK.

Dr. Hunt, as the Director of the Office of Health Research at EPA, you had firsthand experience in bridging the gap between research and regulatory aspects of this problem. What programs did you implement at EPA to address the problems of chemical and environmental hazards to human reproduction?

Dr. HUNT. I probably need to call on my memory here a bit. It was toward the end of my tenure in that position, I carried out a reorganization to insure that the scattered efforts at reproductive research could be brought into a central and more coordinated and flourishing activity. I think that certainly has come to pass. A branch was established to begin with and, subsequently, it was developed to a Division of Reproductive Biology. I imagine that Dr. Heuter, who is going to speak for EPA, will be able to comment on that further.

The efforts during those years were also to insure that some preference would be given to reproductive research. I felt very strongly that I should attempt to redress the imbalance of the past, that we were, as a regulatory agency, being continually bombarded with problems related to reproduction in populations exposed to a variety of environmental hazards, be it in pesticides, toxic substances. So, I would hope that my period with the Agency, both with the Science Advisory Board and with the Office of Health Research, did, in some way, redress that imbalance in that Agency.

Mr. GORE. What is your assessment of the current status of these programs at EPA?

Dr. HUNT. I have not gotten a recent update on the budget allocation for this year and the next year. I can only speak to the general tenor of the times. I think that I would speak in the more positive vein here that we must hold what we have under all circumstances, that the faith and the confidence that I have in the scientists in the area of reproductive research in the Federal agencies—not just EPA, but in the Federal agencies—particularly in EPA, the quality of that work is extremely good. The view overall, I believe, of what needs to be done is to insure a balanced research environment. The academic community runs somewhat as a flywheel on all of this, we do our research in areas that we are interested in. Scientists and administrators in these regulatory agencies just

have to be sophisticated in understanding how that is affecting their decisions.

Mr. GORE. All right.

Let me ask the panel about two specific hazards, and ask you to respond as expert witnesses. Are you familiar with the reproductive hazards associated with anesthetic gases? Dr. Manson, how would you assess the reproductive hazards of anesthetic gases?

Dr. MANSON. There have been a number of broad-based epidemiological studies on operating room personnel as well as dentists and dental assistants which have indicated that, at the time these studies were conducted, the incidence of spontaneous abortion, as well as birth defects to a lesser extent, were elevated in female workers in the operating room.

There have been a number of studies on the pregnancy outcomes of spouses of male operating room personnel. Initial studies indicated that there was an association between exposure of the male in the operating room and adverse pregnancy outcome in the spouse. This finding has not been substantiated by additional followup studies.

Anesthetic gases are amongst the most extensively studied environmental agents in terms of their impact on reproduction, and a clear association has been found between operating room exposure and spontaneous abortion outcome.

Today I have heard that many operating rooms employ scavenger systems to protect personnel by removing waste anesthetic gases from the operating room. I believe that today the problem is not as great as it was at the time these studies were conducted.

Mr. GORE. But it is clearly a reproductive hazard associated with adverse outcomes?

Dr. MANSON. Exposures at the levels that were encountered in the populations that were studied were clearly a hazard to reproduction.

Mr. GORE. Does any other witness want to respond to that? Does anybody disagree with that assessment? Everybody agrees with that assessment. Dr. Nisbet, did you want to respond?

Dr. NISBET. Yes. In our report, we reviewed the various studies on anesthetic gases, and we agreed very closely with Dr. Manson's evaluation. It did seem to us rather striking how much more attention had been paid to anesthetic gases than to the general body of occupational exposures, and we had a suspicion that the medical community was more interested in hazards that sisters and brothers were exposed to than they might have been in the wider population of exposed workers.

Mr. GORE. But for whatever reasons, the work was done. It was done and did establish that this is clearly a reproductive hazard of a serious nature associated with adverse outcomes.

What about ethylene oxide? Is anybody familiar with that?

Dr. HUNT. Generally, I think that ethylene oxide is presenting to us an additional example of the environment of the hospital which is to have been viewed as less important in occupational health than the industrial setting. Ethylene oxide itself has been shown to be related to cytogenetic changes in those exposed. There have been some repetitive studies, and perhaps Dr. Bloom would speak to the specifics of that.

I would comment, however, on the peculiarity of the social environment of the hospital. We have had now several situations—the anesthetic gas one, rubella, ethylene oxide, and a whole raft of others—wherein the occupational health constraints have not been laid on hospital administrations to insure that the many service workers in that setting are protected as well as those in industry.

Mr. GORE. Dr. Bloom?

Dr. BLOOM. The story with ethylene oxide from a genetic point of view is, I think, very interesting, in that the descriptions that have emerged and that are now being confirmed in repeat studies are that ethylene oxide in exposed workers, workers who handle materials for sterilization primarily in hospitals, show an increase in the frequency of damage to the chromosomes which is a particular form of damage called cystochromatid exchange. That is an exchange between two arms of the chromosome.

The interesting aspect of this is that the formation of these exchanges is thought to correlate reasonably well with the production of specific kinds of single gene alterations, so that when a chemical like ethylene oxide produces this kind of alteration, it is thought then to be a piece of evidence that suggests it is mutagenic.

Johnson & Johnson is conducting epidemiological studies on ethylene oxide to look at reproductive outcomes in workers who have been exposed to this compound which may well be mutagenic, but it raises the question of what is the relationship between the mutagenicity as seen in the cells of the workers and the possible reproductive hazards to which they may be subjected. I think that the answer is that we don't know. In other words, it is suggestive that because the compound is mutagenic and because there are somatic cell chromosomal abnormalities produced, that does raise the index of suspicion about possible reproductive hazards, but it doesn't lock it in. That is where the epidemiologic evidence will be required.

Mr. GORE. Fine.

Mr. Walker.

Mr. WALKER. Thank you, Mr. Chairman.

Do we have a way of isolating the effects of workplace exposure to a single chemical agent from the chronic low-level exposure to a variety of hazards in the environment?

Dr. BLOOM. There have been a number of studies. I think, for example, the ethylene oxide is one such study. There certainly have been numerous studies, and perhaps they are the best ones that I could mention in terms of them being well-controlled studies, in terms of radiation workers in which people working with varying amounts of radioisotopes and radiation workers in industry of various sorts have been shown to have chromosomal abnormalities in their body cells in proportion to the dose to which they were exposed.

Those studies are only validated when other environmental factors that are capable of causing those kinds of changes in the cells have been controlled for. In other words, there are many agents in the environment normally that can cause this kind of damage. Certainly a well-controlled epidemiological study will answer the question when there is a recognized agent at doses which can be reasonably well quantified. So, I think one can make the distinction in a

number of instances, and radiation studies would be a good example of that, and the ethylene oxide is another.

Mr. WALKER. So the answer to my question is that, yes, there is some limited data to show that you can in fact isolate, but that it is not something which has been done on a broad scale at this point and that there are not accepted techniques for doing it.

Dr. BLOOM. That is correct.

Dr. Nisbet?

Dr. NISBET. A well-controlled epidemiological study involves a rigorous comparison between a group of exposed people and a group of controls which is selected to be as similar as possible to the exposed group, except in respect to the fact of exposure. Occupation-exposed workers provide some of the best opportunities to identify groups with specific single exposures to single chemicals. Very often, workers are exposed to a variety of chemicals in the workplace where you can find a group of workers who have worked with the same chemical for a substantial period. This offers a very good opportunity to definitive epidemiological studies.

Of course, the control group, the comparison group, has been exposed to a variety of chemicals in their daily lives and in the environment. So it is necessary to match as closely as possible for confounding exposures such as smoking and drinking alcoholic beverages. But when you do that, a well-controlled epidemiological study with a single exposure can provide you very definitive information.

What is unfortunate is that this opportunity has not been exploited in very many cases. Industry, as a whole, includes very many groups of workers exposed to single chemicals who could be studied in this way but have not yet been.

Mr. WALKER. The logical follow-on question is: What is the state of our knowledge with regard to the combined effects of a variety of chemical agents that we are all exposed to and how they interact? That becomes, then, a key to whether your epidemiological studies on single agents can in fact be validated.

Dr. BLOOM. I think one of the answers to that is that we don't really know. I think that when we talk about spontaneous abortion rates, congenital malformation rates, rates of chromosomal damage, those are reflections of many things in the society. I think that we don't have data on how many of these chemicals interact when there is multiple exposure. I think that the answer is that we are trying, and there is a need for baseline data to establish what it is in the normal human population in terms of some of these parameters, chromosome damage, spontaneous abortion, et cetera, and if there is a single exogenous agent that can be assessed, then it is reasonable to do that.

But I think that when you are dealing with multiple exposures in the environment, there is no way we are ever going to be able to really well sort out, for example, what percentage of all spontaneous abortions is caused by smoking by the mother, what percentage is due to alcohol consumption. I think we are not going to be able to do that. We will get a baseline on these parameters for our society and not much else.

Mr. WALKER. Dr. Hunt?

Dr. HUNT. I think your question also relates to the issue of assessment of exposure and the fact of the high cost of monitoring

levels of contaminants in the human body to give you some indication of past exposure or current exposure. Certainly the lead standard has highlighted that in industry, how much does it cost to run the monitoring program. That is the easiest. To run lead assessments is relatively simple and quite cheap. But when you come to speak of pesticide residues in breast milk, for example, there is no way that we can at the current cost of chemical analysis run around the country and do that on a broad scale. There are some very intensive studies going on in that area, as will be reported later. But the fact is that it costs an astronomical amount for the information to insure that you know what the contamination of the population is. It would again lead me to a recommendation that the development of more rapid, cheaper analytical techniques would solve an incredible number of problems in the epidemiologic world.

Mr. WALKER. Dr. Manson?

Dr. MANSON. This issue of multiple exposures, as best embodied by the problem of toxic waste dumps—which is the most extreme case of multiple exposures we can imagine—has defied the traditional analytical approach in which the potential for adverse health effects is determined by measuring the level of exposure in the environment, and in tissues of exposed subjects. This approach has not been possible in toxic waste dump areas because of the multiplicity of exposures.

An alternative approach proposed by the NIEHS, in a new grants program is the development of sensitive human clinical tests, or noninvasive tests that can be applied to large populations to ascertain the state of their reproductive health, the state of respiratory health, cardiovascular health, et cetera. This is a completely opposite approach than to measure levels of chemical exposure, as we normally have.

Mr. WALKER. What I am coming to is that it is obvious that human reproductive issues and the whole business of the hazards involved is something that we have got to be concerned about. How close are we to being able to draw conclusions?

Dr. MANSON. Regarding what?

Dr. HUNT. I think we can already conclude that certainly in the occupational setting, the known reproductive toxins should be controlled as assiduously as we apply that concept to carcinogens in the area of drug testing and such, and that reproductive testing should continue.

We already have the template laid out. The template is there for what we need. The balance, in my view, has to be maintained over a long period of time because, if we found the perfect answer to your question tomorrow or next week, 5 years from now, it would probably be different because there would be a new environment, a new world, and new questions being asked.

Mr. WALKER. Spoken like a good scientist.

Dr. HUNT. Yes. But who would know that 20 years ago—and let's say a few more years when we were born—that our parents were as concerned about our perfection and that of our siblings as our children are today. Our children are expecting to have their babies, one maybe, two maybe, and they have to be perfect children. We have got a whole different concept of quality control today.

Mr. WALKER. Dr. Nisbet?

Dr. NISBET. I would like to jump into this issue, too, because we did address this in the CEQ report 2 years ago. We were asked, in fact, by CEQ to form some kind of scientific assessment of the magnitude of the problem of chemical hazards to human reproduction—in other words, to essentially answer your question. We came out with the conclusion that, yes, there was indeed a substantial public health problem of reproductive impairment, and there was a substantial known interaction between chemicals and human reproductive impairment. But our conclusion was then that the degree of overlap between the states of knowledge on those two aspects was not too great. Where they did overlap, where you did have good information on substantial human exposure to reproductive toxic agents, then we did have some clear indication that there was a problem. That comes up in drugs, it comes in occupational chemicals, and it comes up in chemicals of abuse in the general lifestyle such as cigarette smoking and alcohol.

So, our conclusion was and remains that, yes, there is substantial indication of a real problem with chemicals in human reproduction, at least at the high end of human exposure. We don't know how far down the scale of human exposure that progresses, so we could not—I don't think there is enough scientific information now to establish the importance of chemicals in the environment to the general population's reproductive performance.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. GORE. One final question: Would all of you agree that this is a prime candidate for interagency cooperation in attacking this problem?

Dr. NISBET. Yes.

Mr. GORE. The IRLG was formed in order to provide a mechanism for such cooperation, and that has now been disbanded; is that correct?

Dr. HUNT. Yes.

Mr. GORE. Dr. Hunt, specifically, just to take the example of epidemiology, when you were at EPA—and correct me if I am wrong in summarizing this—you were less than satisfied with the in-house capability for epidemiology at EPA and began the process of phasing out EPA's epidemiology, partly because you felt that the interagency cooperation could compensate; is that correct so far?

Dr. HUNT. Yes.

Mr. GORE. With the disbanding of IRLG and the diminished level of cooperation between agencies, do you think that decision ought to be reassessed by the current EPA?

Dr. HUNT. Yes, I certainly do. Although, I doubt the decision would come out to be much different at this stage. Let me talk about it in budget terms and long-range terms. The epidemiology research that EPA was able to mount, given the dollars available, tended to have diminished to a level where we were still able to fund descriptive studies which give you a good idea for a larger study. But certainly the funding available for epidemiology was not going to allow for the testing of those hypotheses. It was reasonable to expect that with the cooperative climate of several years ago, the working together of epidemiologists in the National Cancer Institute on cancer epidemiology, in heart and lung and respiratory epidemiology, where they had resources very specifically directed

to that and the cooperation to piggyback environmentally related studies onto their big studies, we had the best use of research dollars available to us.

As it turns out today, I would emphasize more the fact that that reasoning is what went into the decision, not so much the issue of absolute dissatisfaction. It was the inability to increase and improve the epidemiologic activity in the agency with the funds available.

Mr. GORE. OK.

Do you have any other questions, Mr. Walker?

Mr. WALKER. No, Mr. Chairman.

Mr. GORE. I would like to thank all of you for appearing here. We are going to have to move on to our next panel. Thank you very much for getting us off to a good start.

Without objection, we will hold the record open at this point for inclusion of those portions of the CEQ study that the majority and minority staff select, the rather lengthy summary and other portions that we can put into the record.

[The information follows:]

EXECUTIVE SUMMARY

Scope of This Report (Chapter I)

This report explores the importance of chemicals as factors contributing to reproductive impairment in the human population. It summarizes the results of studies in exposed humans, surveys methods for testing chemicals in laboratory animals, and discusses the predictive value of animal tests. It also summarizes actions taken to regulate chemical hazards to reproduction, and lists policy issues raised by the facts under review. Although the report is not an exhaustive review of the scientific literature, its findings suggest that the relationship between exposure to chemicals and human reproductive impairment may be an important area of public health concern that deserves more scientific investigation and evaluation.

The Human Reproductive System and its Susceptibility to External Agents (Chapter II)

Human reproduction requires the interaction of complex anatomical, physiological, and behavioral systems, all of which must function unimpaired and in correct sequence if reproduction is to be successful. The first part of Chapter II describes the susceptibility of each stage and process in the male and female systems to the action of toxic chemicals. Table II-1 provides a schematic summary of the types of adverse outcomes (end points) likely to arise from actions at each stage. Action at any one stage may give rise to a number of different end

points, and any one end point can result from a variety of actions occurring at a number of different stages. Further research is needed to extend a knowledge of the inter-relationships among different end points, and between end points and mechanisms of action. Reproduction involves more processes in females than in males, and some processes in females include critical periods of differentiation and development. However, it does not necessarily follow that females are more sensitive to the action of any given agent.

Sources of Statistical Information on the Occurrence of Reproductive Impairments in the U.S. Population (Chapter III)

Chapter III lists a number of large sets of data that are maintained on the frequency of various types of reproductive outcome in the U.S. population, and on the occurrence and distribution of various types of reproductive impairment. Some sets of data are compiled for routine statistical purposes, some for surveillance purposes, and some for research. The primary sources of data are records of vital statistics and physicians' and hospital records. Although complete and accurate data are collected on some types of outcome (e.g., births, birth weight, and infant mortality), data on some outcomes are less reliable (e.g., spontaneous abortions and morphological birth defects), and data are not routinely collected on yet other outcomes (e.g., infertility, early spontaneous abortions and functional impairments). These sets of data are useful in establishing baseline frequencies of occurrence of certain types of impairment, and in revealing

trends and patterns. They are potentially useful for investigating associations between certain types of impairment and "environmental" factors, including chemicals, but they have not often been used for such purposes. The present systems for recording reproductive impairment are limited by problems of reliable ascertainment of the end points and by incomplete reporting. Except for such parameters as birth weight, which is routinely and reliably recorded, it is not clear to what extent data from these systems can be used to investigate small differences in the frequency of specific events. These sets of data would be more useful if they were collected more uniformly and systematically, and if more information were collected to permit linkage between records of adverse outcomes and information on exposure to environmental agents, such as drugs, and occupational factors.

The Magnitude of the Problem of Reproduction Impairments (Chapter III)

Reproductive impairments of one kind or another are both frequent and widespread in the U.S. population. Problems that appear to affect millions of couples at one time or another include inability to conceive, spontaneous abortion, premature births, low birth weight, morphological or functional birth defects, and perinatal mortality. Published estimates of the proportion of reproductive attempts that fail or are impaired in one or more of these ways range approximately from 30% to 80%. The large uncertainty arises primarily from the difficulty in measuring the frequency of conception failures and very early spontaneous

abortions. Further research is needed to clarify the frequency of these outcomes, which may be the most important types of reproductive impairment.

The Contributions of Environmental Factors to Reproductive Impairment in the Human Population (Chapters III and IV)

Chapters III and IV describe evidence suggesting that environmental factors are significantly associated with reproductive impairment in segments of the U.S. population. Environmental factors include nutrition, diet, stress, infections, access to and quality of medical care, radiation, and chemicals such as therapeutic drugs, pesticides, cigarette smoking, alcoholic beverages, illicit and addictive drugs, and industrial pollutant

a. The frequency of some types of reproductive impairmen varies widely from state to state and from county to county within the United States.

b. The frequency of some types of reproductive impairment has changed in time, at a rate much too rapid to be explained by genetic changes or changes in other intrinsic factors.

c. In some cases, the frequency of various kinds of reproductive impairment can be associated statistically with various environmental factors.

d. A number of drugs, chemicals, and other environmental factors have been associated with reproductive impairments in exposed groups within the population.

Evidence of a similar nature is available for various kinds of cancer, and has been used to argue that environmental factors

play a major role in the initiation and development of certain cancers. The evidence of this kind for reproductive impairment is considerably less extensive and complete than that for cancers. However, the evidence summarized in Chapters III and IV suggests that environmental factors (in the broad sense discussed above) are substantial contributors to certain types of reproductive impairment. Further research is needed to establish how important they are, and to distinguish which environmental factors contribute to the occurrence of each type of reproductive impairment.

Reproductive Impairment in the Human Population and the Contribution of Chemicals (Chapters III and IV)

Drugs and other chemicals are only part of the broad spectrum of environmental factors that are known or suspected to impair reproductive success in humans, and there is only limited evidence that can be used to estimate their importance. As yet, large-scale surveillance studies have not been used to identify specific chemical hazards to reproduction (Chapter III). Chapter IV (together with Appendix A) summarizes a large number of studies of the effects of specific agents. The results of these studies suggest that cigarettes and alcoholic beverages have important adverse effects in heavy users and may have substantial effects in moderate users. They also show that certain therapeutic drugs (notably thalidomide and diethylstilbestrol) have had important adverse effects, at least in the past, and that workers exposed in the workplace to certain agents (notably anesthetic gases and lead) are at risk. However, only a limited

number of drugs and occupational exposures have been studied for adverse reproductive effects. The evidence available to date that environmental chemicals may have adverse effects in the general population is scanty and inconclusive, except in cases where accidental contamination of food has resulted in unusually high exposure. However, it is difficult to investigat possible effects of widespread, low-level exposure, and very few studies of such effects have been reported. Further researc is needed to establish how many other highly exposed groups are at risk, and whether other general population exposures are significant.

There is much evidence that drugs and other chemicals have had substantial adverse effects on reproduction in highly expose groups. However, cigarettes and alcohol are the only agents reported to have substantial effects in the general population.

Limitations on Human Studies (Chapter IV)

Chapter IV includes a description of the types of study that are used to identify reproductive hazards in human populations, and a brief discussion of their limitations. The practicality of conducting such studies depends generally on the ability to identify an exposed group and document its exposure. This is generally easiest for prescription drugs, whose use is usually recorded; relatively easy for cigarette smoking and alcohol, for which individuals determine their own pattern of use and can document it fairly reliably; fairly difficult for occupational exposures, for which exposed individuals can usuall

be identified but for which the magnitude of exposure is usually difficult to estimate; and very difficult for environmental chemicals, for which both the distribution and magnitude of exposures are difficult to document. Even when exposed groups can be identified, it is often difficult to investigate their reproductive performance unless the affected individuals are willing to discuss these issues with researchers. Other practical problems are common to all epidemiologic studies, including problems encountered in selecting appropriate control groups and documenting their exposure, problems of bias, and confounding factors. For these reasons the most effective studies have been of the effects of drugs; studies of occupational and environmental agents have often been controversial or inconclusive.

Provided that attention is paid to these problems, further studies of highly exposed groups are likely to be useful in identifying specific risk factors. Human epidemiologic studies of industrial groups may be an effective way to establish the safety or hazard of specific chemicals. However, it should be recognized that such studies are inherently difficult to conduct with general environmental pollutants, and that any effects that such agents may be causing in the population are unlikely to be identifiable unless they are unusually conspicuous.

Laboratory Screening Systems (Chapter V)

Chapter V lists a large number of laboratory tests for investigating possible adverse effects of chemical agents on

reproduction. However, at present only three of these tests are in general use for screening chemical agents; these are applied primarily to drugs, food additives, and pesticides. They are expensive to conduct--especially when they have to be run in several species, as part of a multispecies screen--and it is not feasible to apply them to more than a limited number of the potentially toxic chemicals already in the environment or proposed for new uses. In fact, much of our knowledge of the effects in animals of chemicals known to affect reproduction in humans is derived from shorter or simpler tests (see Appendix A).

One important element that is lacking from the existing screening system is a technique for prescreening chemicals, in order to select for full-scale testing those that are most likely to prove hazardous. Such a technique might involve a simple, rapid, in vitro test (analogous to the Ames test for mutagenicity), or application of structure-activity theories to predict likely activity. Although a number of in vitro tests are already available, none appears to be a very strong candidate for this prescreening function. More research and development are needed to improve the efficiency, reliability, and sensitivity of the existing screening systems.

The Use of Laboratory Tests to Predict Human Risks (Chapter VI)

Until more studies can be carried out in exposed groups within the human population, reliance must be placed on laboratory tests to identify potentially hazardous agents. Chapter V

presents a preliminary analysis of the concordance between the results of experimental studies in animals and the reported effects of the same agents in humans. This analysis is based on data for 21 selected agents, as tabulated in Appendix A. The results of this analysis suggest that many (if not most) reproductive impairments identified in humans have close counterparts in one or more species of experimental animals. That is, specific chemical agents that have been found to be teratogenic or to cause other reproductive impairments in humans have been found to produce qualitatively similar effects in one or more test animal species. Furthermore, there is some agreement between the doses reported to be effective in humans and the doses that are effective in the most sensitive animals (see Tables VI-4 and VI-5). With one exception, humans appear to be somewhat more susceptible than the most susceptible animal species tested.

More detailed analysis is needed to confirm or to modify these preliminary findings. Pending such analysis, they tend to suggest that animal tests can predict both the types of effect likely to occur in humans and (to an order of magnitude) the likely range of effective doses, provided that the appropriate species are selected for testing. These findings show promise for the development of methods for quantitative risk assessment. However, it will be difficult to determine in advance which animal species is appropriate in each specific case, and such a predictive system is liable to yield an unknown number of

"false positive" predictions of hazards. The development of a reliable multispecies screening system will require more da on effects in humans and more research in comparative toxicol including studies in comparative metabolism and pharmacokinet

Dose-response Relationships and Risk Assessment (Chapter VI)

Very little has been published on dose-response relation ships for agents that affect reproduction in humans, although such relationships could probably be constructed from data av on the effects of cigarette smoking and alcohol. There appea to be no systematic compilation of dose-response relationshi in animals. For teratogenic agents, dose-response relationsh in animals usually rise steeply after the dose required to pr the first effect is exceeded. This empirical generalization has been used to argue that threshold (safe) doses usually e: for teratogens in animals. However, it is not clear that th assumption of thresholds can be applied automatically to hum More research is needed to establish the characteristics of dose-response relationships in humans, and to establish in w circumstances thresholds can be assumed to exist. Such info is required for risk assessments at doses lower than those a which effects have been observed, and for estimating "safe" or "acceptable" levels of exposure.

Regulatory Authority and Regulatory Actions to Date

The federal government has authority under a number of different statutes to regulate chemicals that pose hazards

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human reproduction. Together with statutes that cover specific classes of chemicals or specific exposure situations, the Toxic Substances Control Act (TSCA) confers authority to regulate essentially all manufactured chemicals. However, TSCA excludes three important classes of chemicals that are known or suspected to pose reproductive hazards: tobacco products, alcoholic beverages, and illicit drugs. Under most of the statutes, the authority to regulate chemicals that pose reproductive hazards is part of a general authority to regulate agents that pose health risks, but some statutes (including TSCA) specify teratogenicity as an effect of especial concern.

Despite this broad authority, only a limited number of regulatory actions have been taken specifically to reduce reproductive risks. The most extensive such actions are those of the U.S. Food and Drug Administration (FDA), which has required labeling of agents known to be teratogenic and will shortly require informational packaging with agents known to pose other reproductive hazards. In a number of regulatory actions, information on reproductive effects was cited in support of the action but appeared to be secondary to information on carcinogenic effects. Recent regulatory actions in which reproductive effects were the primary basis for regulation included: diethylstilbestrol, whose approval for use as an animal drug was withdrawn by FDA; lead, for which a new occupational exposure standard was set by the Occupational Safety and Health Administration; and caffeine, for which FDA has proposed to delete its status as a permitted

food additive and to require further testing. In addition, tolerances set for residues of pesticides in food by the U.S. Environmental Protection Agency in some cases, have been base on data on reproductive toxicity, but the methods for establi tolerances are now under review by the agency. In general, however, regulatory agencies have placed little weight on rep ductive toxicity, devoting much more attention to the regulat of carcinogens. The reasons for this lack of emphasis on reg of reproductive hazards have not been made explicit.

Policy Issues

A number of important policy issues are raised by these findings, including the following:

- the importance of reproductive impairments as a public health problem
- the role played by chemicals in reproductive impairmen
- the reliability of existing methods for identifying ch ical hazards to reproduction
- the lack of accepted procedures for risk assessment
- the scientific basis for regulatory actions
- the differential regulation of exposure to men and wom

Parallel between Reproductive Hazards and Carcinogenic Haza

The present state of scientific knowledge of chemical ha to reproduction is somewhat similar to that of chemical car- cinogens in the late 1960s. If scientific knowledge of rep ductive hazards is developed in an orderly manner, there is an opportunity to avoid some of the controversies that have been raised by regulation of chemical carcinogens.

Key Findings and Recommendations

- This report explores the importance of chemicals as factors contributing to reproductive impairment in the human population. Although it is not an exhaustive review of the scientific literature, its findings suggest that the relationship between exposure to chemicals and human reproductive impairment may be an important area of public health concern. This area deserves more scientific investigation and evaluation. The study recently initiated by the Interagency Regulatory Liaison Group is expected to provide critical and comprehensive reviews of teratological and other data on reproductive hazards. These reviews would be useful and timely.

- Toxic chemicals can exert effects at many different stages in male and female reproduction. Action at any one stage can give rise to a number of different end points, and any one end point can result from a variety of actions occurring at a number of different stages. Although more stages of reproduction occur in females, including critical processes of differentiation and development, it does not necessarily follow that females are more sensitive to any given agent.

- A number of large sets of statistical data are maintained on the frequency and distribution of various types of reproductive outcome. These sets of data are of varying completeness and accuracy, and cover only certain types of impairment. They have not often been used to investigate associations with external factors, but are useful in establishing baseline data and in revealing trends and patterns. These sets of data would be more useful if they were collected more uniformly, and if more information on environmental factors were collected.

- Reproductive impairments of one kind or another are both frequent and widespread in the U.S. population. Published estimates of the proportion of reproductive attempts that fail or are impaired range approximately from 30% to 80%. Further research is needed to determine the frequency of conception failures and very early spontaneous abortions.

- Evidence derived from geographical patterns, time trends, and associations with specific environmental factors suggests that environmental factors are substantial contributors to certain types of reproductive impairment. However, this evidence is considerably less extensive than the similar evidence for the importance of environmental factors in cancer. Further research is needed to establish the importance of environmental factors in reproductive impairment.

- There is much evidence that drugs and other chemicals have had substantial adverse effects on reproduction in highly

exposed groups. However, cigarette smoking and alcohol are the only effects reported to have substantial effects in the general population.

- The practicality of conducting studies in human populations depends on the ability to identify an exposed group and docume its exposure. Other problems encountered in human studies involve the selection of appropriate control groups, eliminati of bias and identification of confounding factors. The most effective studies have been those on the effects of drugs; studies of occupational and environmental agents have often been controversial or inconclusive. Further studies of highly exposed groups are likely to be useful in identifying specific risk factors, but such studies are inherently difficult to conduct with general environmental pollutants.

- A large number of laboratory tests is available for investigat ing possible adverse effects of chemical agents on reproduction. However, only three of these tests are in general use for screening chemical agents. More research and develop ment are needed to improve the efficiency, reliability, and sensitivity of the existing screening systems, and in particul to devise a useful short-term prescreening test.

- A preliminary study of data on 21 chemical agents shows a reasonably close concordance between effects reported in humans and in one or more experimental animal species. With one exception, humans were affected at doses similar to or less than those that affected the most sensitive animals. These findings show promise for the development of methods for quantitative risk assessment. However, it will be difficult to determine in advance which species should be regard as appropriate for predicting likely effects in humans. Any predictive system based on animal tests may yield an unknown number of "false positive" predictions of hazard. The development of a reliable predictive system will require more research in epidemiology and in comparative toxicology.

- Very little has been published on dose-response relationships for agents that affect reproduction in humans. More research is needed to establish their characteristics, and to establis in what circumstances threshold doses can be assumed to exist Such information is needed for low-dose risk assessments, and for estimating "safe" or "acceptable" levels of exposure.

- The federal government has broad authority to regulate chemicals that pose reproductive hazards. Apart from labeling of prescription drugs, however, regulatory agencies have placed relatively little emphasis on reproductive hazards in their recent actions. The reasons for this have not been made explicit.

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- A number of important policy issues are raised by these findings, including the following:
  - the importance of reproductive impairments as a public health problem
  - the role played by chemicals in reproductive impairment
  - the reliability of existing methods for identifying chemical hazards to reproduction
  - the lack of accepted procedures for risk assessment
  - the scientific basis for regulatory actions
  - the differential regulation of exposure to men and women
- The present state of scientific knowledge of chemical hazards to reproduction is somewhat similar to that of chemical carcinogens in the late 1960s. If scientific knowledge of reproductive hazards were developed in an orderly manner, there would be an opportunity to avoid some of the controversies that have been raised by regulation of chemical carcinogens.

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TABLE II-1

RELATIONSHIP BETWEEN THE SITE AND TIMING OF ACTION OF TOXIC AGENTS ON HUMAN REPRODUCTIVE SYSTEM AND THE OBSERVABLE EFFECTS (END POINTS)

Reproductive Stage	Organs and functions potentially affected		Possible End points
	Female	Male	
Germ cell formation	Oogenesis (occurs during fetal development of mother) Gene replication Cell division	Spermatogenesis Gene replication Cell division	Sterility, subfecundity, damaged sperm or eggs, chromosomal aberrations, menstrual effects, age at menopause, hormone imbalances, changes in sex ratio
	Egg maturation Hormonal influence on ovary	Sperm maturation Sertoli cell influence Hormonal influence on testes	
	Ovulation Hormonal influence on ovary		
Fertilization	Oviduct Contractility Secretions Hormonal influence on secretory and muscle cells	Accessory glands Sperm motility and nutrition Hormonal influence on glands	Impotence, sterility, subfecundity, chromosomal aberrations, changes in sex ratio, reduced sperm function

TABLE II-1 (continued)

Reproductive Stage	Organs and functions potentially affected: Female	Organs and functions potentially affected: Male	Possible End Points
Fertilization (continued)	Uterus Contractility Secretions Hormonal influence on secretory and muscle cells Nervous system Behavior Libido	Nervous system Erection Ejaculation Behavior Libido	
Implantation	Uterus Changes in uterine lining Secretions Hormonal influence on secretory cells		Spontaneous abortion, fetal resorption, chromosomal aberrations, subfecundity, stillbirths, low birth weight

TABLE II-1 (continued)

Reproductive Stage	Organs and functions potentially affected		Possible End Points
	Female	Male	
Embryogenesis	Uterus Placenta formation		Spontaneous abortion, other fetal losses, birth defects, chromosomal abnormalities
	Embryo Cell division Tissue differentiation Hormone production Growth		change in sex ratio, stillbirths, low birth weight
Organogenesis	Placenta Nutrient transfer Hormone production Protection from toxic agents		Birth defects, spontaneous aborton and other fetal death, chromosomal aberrations, retarded growth and development, transplacental carcinogenesis
	Embryo Organ development and placement Growth		
	Maternal nutrition		

TABLE II-1 (continued)

Reproductive Stage	Organs and functions potentially affected: Female	Organs and functions potentially affected: Male	Possible End Points
Perinatal	Fetus Growth and development Uterus Contractility Hormonal effects on muscle cells		Premature births, birth defects, (particularly nervous system), stillbirths neonatal death, low birth weight toxic syndromes or withdrawal symptoms in neonates
	Maternal nutrition		
Postnatal	Infant survival		Mental retardation, infant mortality, retarded development, metabolic and functional disorders developmental disabilities (e.g., cerebral palsy and epilepsy)
	Lactation		

MR. GORE. Our second panel includes Dr. J. Donald Millar, Director of NIOSH; and Dr. Charles E. Carter, Scientific Director of the National Institute of Environmental Health Sciences.

Without objection, the prepared text of the witnesses from this panel will be put in the record at this point.

Dr. Millar, we want to welcome you. Thank you for being here. We invite you to proceed.

STATEMENTS OF DR. J. DONALD MILLAR, DIRECTOR, NATIONAL INSTITUTE OF OCCUPATIONAL SAFETY AND HEALTH, CENTERS FOR DISEASE CONTROL, ATLANTA, GA., AND CHARLES E. CARTER, SCIENTIFIC DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, RESEARCH TRIANGLE PARK, N.C.

Dr. MILLAR. Thank you, Mr. Chairman. I would like to make a somewhat abbreviated statement.

I am J. Donald Millar, M.D., Director of the National Institute for Occupational Safety and Health of the Centers for Disease Control. I am delighted to be here with you to discuss a problem which we find quite important, because we feel very strongly that it is a role of NIOSH to attempt to understand and prevent work-related hazards which can affect the ability of men and women to have normal healthy children.

As you know, NIOSH was established by the Occupational Safety and Health Act in 1970. As part of the Centers for Disease Control, NIOSH has worked closely with other organizations, both inside and outside the Centers, in collaborating with other organizations that have competency in cytogenetics and reproductive health. The act authorized NIOSH to conduct research, to develop recommendations to the Department of Labor for occupational safety and health standards, to conduct health hazard evaluations at the request of employees and employers, and also to conduct training and educational programs.

As you have heard this morning, Mr. Chairman, in the United States, little attention was directed toward workplace hazards to reproduction until the mid-seventies. NIOSH initiated laboratory and epidemiologic investigations of chemical reproductive hazards in 1974 and, since that time, this area has become a major part of the NIOSH research effort.

During the early years of research on reproductive hazards of work, we emphasize the hazards to women workers and the potential dangers to the developing fetus from exposures to the mother. In 1977, however, the highly publicized incident, referred already to by the chairman, turned the attention of both researchers and the public to the potential for workplace exposures to produce serious reproductive effects in men. There was a health hazard evaluation conducted by us in a California pesticide plant which helped to confirm that workplace exposure to dibromochloropropane, DBCP, a chemical used to control worms that infest farmland, was responsible for a number of health effects, including sterility, in male workers who were exposed to the substance during its formulation. This finding led to the development by OSHA of an emergency standard for occupational exposure to DBCP. Perhaps more impor-

tantly, it demonstrated both to the scientist and to the thoughtful laymen that some relatively short-term exposures in the workplace could produce detrimental reproductive effects in men.

The range of effects of reproductive hazards can be divided into three broad categories that I think are worth reiterating at this point. The first includes detrimental effects on the ability to conceive: Impotency, reduced libido, altered sperm function in men, altered germ cell maturation, and altered ovulation and menstruation in women. The second category includes detrimental effects on the ability to carry a pregnancy to a normal, full-term delivery, resulting in death of the fetus in utero, spontaneous abortion or stillbirth. These results can be brought about by maternal or paternal exposure. The third category includes the production of infants with low birth weight—which is associated with increased infant mortality—with birth defects, and possibly with developmental defects which may become manifest later.

Currently, NIOSH is conducting investigations of work-related hazards to reproductive health in a number of areas, but our efforts are in three principal areas. The first is in laboratory research; the second is in surveillance and epidemiological field investigations; and the third in support of extramural research grants. I would like to say a word or two about each of these three.

First of all, laboratory studies. As a member of the national toxicology program, NIOSH conducts initial screening of chemicals to identify those that appear in short-term animal tests to have adverse effects on reproduction. We then recommend to NTP that these chemicals be subjected to further in-depth laboratory studies. We are the lead agency for comprehensively evaluating reproductive or developmental toxicity of chemicals by animal inhalation studies.

As stated in the report by the Council on Environmental Quality, "most chemicals to which humans are exposed have not been tested for effects on reproduction." The reasons for this include, first of all, the large number of such substances; second, the costs of the tests involved; and third, the extensive time required for testing. Last year, we initiated several projects to develop improved or more rapid, or less expensive tests. These projects included developing an objective, verifiable method of evaluating sperm motility and investigating the feasibility of using fruit flies for prescreening tests of chemicals for teratogenic potential.

We have also evaluated in laboratory animals the reproductive effects of radio frequency and microwave radiation and of some 60 individual chemical compounds, including groups of structurally related compounds. In the laboratory, we have also studied interactions of compounds and complex mixtures.

In the area of surveillance and epidemiology, I want to note that surveillance and epidemiology involve the process of gathering and analyzing data on the prevalence and severity of disorders, and also defining risk factors. You have heard something this morning about the difficulties encountered in this sort of work in this particular area of health.

NIOSH is now working with two State health departments to assemble surveillance data that may be useful for epidemiologic studies of reproductive effects. In an agreement with the health depart-

ment of the State of Utah, we are funding an effort to include information on parental occupations on the birth certificates for all children. If an association between malformations an a particular parental occupation is found, epidemiologic studies may be needed.

VIA another cooperative agreement with the New York State Health Department, NIOSH is funding a project to determine whether particular parental occupations are associated with birth defects in children.

These agreement will help encourage State health agencies to become more involved in the surveillance of reproductive disorders, leading to a clearer definition of the problem.

Turning to our support of extramural research grants, we would like to bring to your attention the fact that the Institute issued a special solicitation in June of 1980 for proposals for extramural research in this area.

The announcement stimulated nearly 100 grant applications. Unfortunately, we were able to fund only 4 grants this year, with a total annual budget of approximately $300,000; that is roughly $1 million over 4 years.

In terms of future directions, Mr. Chairman, I believe we are at the threshold of new understanding about reproductive effects of workplace exposures.

In less than a decade, there has been great progress in development laboratory tests, surveillance, and epidemiological techniques. There are, however, several identifiable activities that could significantly expedite and enhance our understanding.

Expanded surveillance activities, as you have already heard, will be essential to define the scope of the problem. Our cooperative agreements with States and other surveillance efforts are aimed at accomplishing this. Additional reliable methods for screening chemicals and physical agents are clearly important, as are methods to estimate the risk to workers.

Finally, we must continue to raise the level of awareness in researchers, employers and workers to the potential for workplace exposures to substances which affect reproductive function.

We will continue to disseminate new information as it is developed.

I believe NIOSH is in a unique position to make a significant contribution to resolving the problems we have been discussing this morning. Among research agencies, only NIOSH has the statutory right of entry to the workplace. NIOSH has what I consider a unique interactive program of laboratory investigation and epidemiological field investigations.

Because of our expertise, both in field epidemiology and industrial hygiene, I think we have an opportunity to make special contributions in the area of dose response relationships in human exposures.

Our program of investigating health hazards, in response to the requests of workers, employers and official agencies, puts us in a unique position to detect new problems as they emerge.

Our activites in recommending standards and in educating and disseminating information also give us some hope of preventing work-related problems of reproduction.

Indeed, prevention is the ultimate objective of all of our efforts.

Mr. Chairman, this concludes my overview of the involvement of NIOSH in occupational reproductive hazards, and some assessment of some of the future needs in this field.

I would be happy to try to answer any questions you or members of the subcommittee may have, and also to point out that I have with me in the audience today, Dr. Harris, Mr. Hardin, Dr. Rosenberg, and Dr. Chandler, each of whom are more expert in these areas than I.

Thank you.

[The prepared statement of Dr. Millar follows:]

TESTIMONY OF J. DONALD MILLAR, M.D.

Mr. Chairman and members of the subcommittee, I am Dr. J. Donald Millar, Director of the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. With me today are Dr. Elliott Harris, Deputy Director, NIOSH, and Dr. Bryan Hardin, Research Biologist, Division of Biomedical and Behavioral Sciences, NIOSH. I am pleased to testify today about the role of NIOSH in the effort to understand and control the potential for workplace exposures to chemicals and physical agents which can affect the ability of men and women to have normal, healthy children.

As you know, NIOSH was established by the Occupational Safety and Health Act of 1970. It is part of the Centers for Disease Control of the Public Health Service, in the Department of Health and Human Services. NIOSH works closely with other organizations within CDC (the Center for Environmental Health and the Center for Health Promotion and Education) that have competency in cytogenetics and reproductive health. The Occupational Safety and Health Act authorizes NIOSH to conduct research; to develop recommendations to the Department of Labor for occupational safety and health standards; to provide technical assistance and Health Hazard Evaluations to employees and employers; and to conduct and support training and education programs.

In the United States little scientific attention was directed toward workplace hazards to reproduction until the mid-1970s. NIOSH initiated laboratory and epidemiologic investigation of chemical reproductive hazards in 1974, an area that has since become a major part of NIOSH research.

In 1976, NIOSH co-sponsored a Conference on Women and the Workplace, which highlighted results of early studies by the Institute and others, and identified areas in which additional research was needed. In 1977 we published "Guidelines on Pregnancy and Work," a research report to help practicing obstetricians assemble and interpret information necessary for making appropriate clinical recommendations to pregnant workers. In 1978 we supported a second conference on reproductive hazards, this one emphasizing the methods for assessing work-related reproductive hazards.

During the early years to research on the reproductive hazards of work, we emphasized the hazards to women workers and the potential dangers to the developing fetus from exposures to the mother. In 1977, however, a highly publicized incident turned the attention of both researchers and the public to the potential for workplace exposures to produce serious reproductive effects in men. A Health Hazard Evaluation conducted by NIOSH in a California pesticide plant helped to confirm that workplace exposure to dibromochloropropane (DBCP), a chemical used to control a class of worms that infest farmland, was responsible for a number of health effects, including sterility, in male workers who had been exposed to the substance during its formulation. This finding led to the development by OSHA of an emergency standard for occupational exposure to DBCP. Perhaps more importantly it demonstrated both to the scientist, and to the thoughful layman, that some relatively short-term exposures in the workplace could produce detrimental reproductive effects in men.

The range of effects of reproductive hazards can be divided into three broad categories. The first includes detrimental effects on the ability to conceive: impotency, reduced libido and altered sperm function in men, altered germ cell maturation, and altered ovulation and menstruation in women. The second category includes detrimental effects on the ability to carry a pregnancy to a normal, full term delivery, resulting in death of the fetus in utero, spontaneous abortion and stillbirth. These results can be brought about by maternal or paternal exposure. The third category includes the production of infants with low birthweight (which is associated

with increased infant mortality), with birth defects, and possibly with developmental deficits such as learning disabilities, which may become manifest years later.

Currently NIOSH is conducting laboratory and epidemiology studies and supporting research grants in a wide range of reproductive health projects.

LABORATORY STUDIES

As a member of the National Toxicology Program (NTP), NIOSH conducts initial screening of chemicals for reproductive effects. Through this effort NIOSH identifies chemicals that appear, in short term animal tests, to have adverse effects on reproduction. We then recommend to NTP that these chemicals be subjected to further in-depth laboratory studies. NIOSH is the lead agency for conducting comprehensive evaluation of the reproductive or developmental toxicity of chemicals through animal inhalation studies. As stated in the report by the Council on Environmental Quality, "most chemicals to which humans are exposed have not been tested for effects on reproduction." Reasons for this include the number of such substances, the cost of tests, and the extensive time required for testing. Last year we initiated several projects to develop improved or more rapid, less expensive tests. These projects included developing an objective, verifiable method of evaluating sperm motility and investigating the feasibility of using fruit flies for prescreening tests of chemicals for teratogenic potential.

To date NIOSH has evaluated the reproductive effects, in laboratory animals, of radio frequency and microwave radiation and of 60 individual chemical compounds, including groups of structurally related compounds. We have also studied interactions of compounds and complex mixtures. In another area of laboratory analysis, the Institute is examining the mutagenic potential of numerous compounds.

One series of NIOSH studies of structural related compounds, ethylene glycol derivatives, revealed that exposed male animals became less fertile and developed abnormalities of sperm. Studies of one glycol derivative called 2-ethoxyethanol found significant increases in birth defects, retarded growth, and embryonic death in the offspring of pregnant animals exposed at approximately the OSHA Permissible Exposure Limit (PEL). The offspring of animals exposed at about one-half the OSHA PEL exhibited behavioral abnormalities. Glycols are used in solvents, hydraulic fluids, industrial cleaning solutions, and many other consumer and industrial products. NIOSH estimates that more than 1.5 million workers may be exposed to the substances in the workplace.

SURVEILLANCE AND EPIDEMIOLOGY

Surveillance and epidemiology is the process of gathering and analyzing data on the prevalance and severity of diseases and disorders. The goal of NIOSH reproductive hazards research is to identify reproductive disorders that may be occupationally related.

In two surveillance efforts now under way, NIOSH is working with State health departments to assemble data that may be useful for studies of reproductive effects. In an agreement with the Health Department of the State of Utah, NIOSH is funding an effort to include information on parental occupations on the birth certificates for all children born in the State. A second phase involves searching the State's data to identify the occupations of the parents of children born with birth defects. If an association between malformations and particular parental occupations is found, epidemiologic studies in those occupations or laboratory studies of specific chemicals involved in those occupations may be needed.

In a cooperative agreement with the New York State Health Department, NIOSH is funding a State project to conduct telephone followback surveys of women whose occupation on their children's birth records is given as "housewife" or described similarly. The State suspects that although many of the women were not employed outside the home when their children were born, they may have been employed outside the home until shortly before they gave birth. The State will ask the women about their employment for the period from three months before pregnancy through the second trimester of pregnancy and will add this information to the birth records of their children. An attempt can then be made to determine whether particular parental occupations are associated with birth defects in the children.

The NIOSH resources and guidance available to the States in these agreements provide an incentive for States to collect, in easily retrievable form, data that can be invaluable in identifying potential reproductive hazards in the workplace. The agreements also will help encourage States to become more involved in reproductive surveillance.

Two major data bases assembled over the years by NIOSH are also being used to help identify industries and chemical compounds that might be associated with reproductive hazards. One is the data from the Institute's National Occupational Hazards Survey, conducted in 1972 to 1974 to tabulate potential exposures of more than 500,000 workers at approximately 4,600 worksites. The other is the NIOSH Registry of Toxic Effects of Chemical Substances, a compilation of more than 54,000 chemical compounds for which there is at least one toxicity citation in the scientific literature. This Registry lists the lowest reported dose effect relationship for each compound. NIOSH has identified more than 1,800 substances in the Registry for which at least one animal or one human teratogenicity or other reproductive effect has been reported. While the Registry identifies chemicals with reported reproductive effects, it is not intended to provide definitive links between toxicity information and worker health risk.

Using the National Occupational Hazards Survey data base, we will attempt to determine in what industries these substances are used and how many workers may potentially be exposed to them. In addition, the Institute is completing a new, large scale study of 700,000 to 800,000 workers in 5,000 worksites to update the information from the 1972–74 survey. The information from this new National Occupational Exposure Survey will also be combined with the data from the NIOSH Registry.

In addition to the NIOSH reproductive health surveillance of workers, CDC's Center for Environmental Health (CEH) is studying the potential adverse effects of environmental exposures on reproductive health in the general population. The CEH Birth Defects Monitoring Program, the nation's largest reproductive epidemiology surveillance effort, monitors approximately 20 percent of the births in the United States to help understand the etiology of birth defects. The CEH Metropolitan Atlanta Congenital Defects Program includes a pilot study of potential environmental causes of mental retardation. The Center also provides technical assistance to State and local health departments in evaluating particular incidents in which there are suspected associations between environmental exposures and spontaneous abortion, stillbirth, low birthweight, infant mortality, and birth defects.

NIOSH reproductive epidemiology has included studies of pharmaceutical workers exposed to synthetic estrogens, rayon manufacturing workers exposed to carbon disulfide, and hospital workers exposed to waste anaesthetic gases.

In one study now underway, about 500 wives of male lead workers in a battery plant are being asked to provide information about pregnancies and birth defects in their children. They will also be asked about their work histories. The battery plant is providing NIOSH with work histories and medical information, such as blood lead levels, for the women's husbands.

The study will help NIOSH evaluate the extent to which exposures of the father to lead in the workplace may cause abnormal reproductive experience in the mother and birth defects in children. Although lead has been known for many years to interfere with normal reproduction in women and to cause birth defects in the children of exposed women, the study of reproductive effects of paternal lead exposure is relatively new. This study is in the final stages of completion.

REPRODUCTIVE HAZARDS RESEARCH GRANTS

As a further result of NIOSH concern for potential reproductive effects from workplace hazards, the Institute issued a special announcement in June 1980 to solicit proposals for research grants in this area. The announcement detailed the need for epidemiology, biometry and toxicology studies, and experimental laboratory investigations. It also solicited proposals for studies of technology to control exposures to reproductive hazards and for health education and demonstration projects. The announcement stimulated nearly one hundred grant applications. This year NIOSH funded four grants with a total annual budget of approximately $300,000. With the Subcommittee's permission I will submit a copy of the announcement for the record.

FUTURE DIRECTIONS

Occupational health and safety specialists believe we are at the threshhold of new understanding about the reproductive effects of workplace exposures. In less than a decade, there have been considerable improvements made in laboratory test methods, surveillance data bases, and epidemiologic techniques. Progress from this point will involve some trial and error, some false starts. There are, however, several identifiable activities that could significantly expedite and enhance our understanding.

Expanded surveillance will help quantify all facets of the problem. These systems will include, among other things, tabulation of not only the easily identifiable mani-

festations of reproductive disorders, such as birth defects, but also the "hidden" manifestations, such as spontaneous abortions, altered menstrual cycles, and altered ratios of male to female births. More information about the work histories of the parents on the birth records of children will also be invaluable. Our cooperative agreements with States and other surveillance efforts are a step toward accomplishing these goals.

Developing additional reliable, validated methods for screening chemicals and physicial agents that may pose reproductive hazards is also important. We need to increase the accuracy with which results from these tests may be applied to estimate the risk to workers' reproductive health.

Finally, we need to continue to raise the level of awareness in researchers, employers, and workers about the potential for occupational exposures to some substances to detrimentally affect reproductive function. We need to disseminate and exchange important new information as it becomes available. NIOSH is continuing its leadership role in this effort. Last May the Institute co-sponsored a national conference to summarise the state of the art in reproductive toxicology and epidemiology and to suggest directions for future research.

NIOSH is in a unique position to make a significant contribution to all of these areas. Among research agencies, only NIOSH has statutory right to entry to the workplace and an interactive program of laboratory and epidemiology studies in worker reproductive health. In the Institute these two disciplines uniquely reinforce and validate each other. The Institute has a special capability to identify occupationally related reproductive health problems and to communicate this information to the scientific community, employers, and workers.

It is significant that even as our understanding of occupationally related reproductive disorders grows, the population of workers of reproductive age is also growing. According to U.S. Bureau of the Census statistics, 63 percent of the labor force of 86 million were of reproductive age in 1970; that is, between the ages of 16 and 44. In 1978, 69 percent of a larger labor force of 102 million were of reproductive age.

The awareness of workers about the potential for reproductive hazards may also be increasing however. In the early years of NIOSH's Health Hazard Evaluation program virtually no requests for evaluation involved reproductive hazards. In fiscal year 1981 approximately 40 requests included a reproductive health component out of more than 400 requests received.

Mr. Chairman, this concludes our overview of NIOSH's involvment in occupational reproductive hazards research and our assessment of future needs in this field. I would be happy to try to answer any questions you or members of the Subcommittee may have.

Mr. GORE. Thank you very much. We will hold up on questions until Dr. Carter has completed his statement.

Dr. Charles Carter, Scientific Director of the National Institute of Environmental Health Sciences. Welcome and please proceed.

Dr. CARTER. Thank you, Mr. Chairman.

Let me just briefly say a few things about how NIEHS is organized to carry out its responsibilities.

At the outset, I would like to emphasize that we are highly dependent upon interaction with other agencies. The ties to the basic biomedical science community must be extraordinarily strong for us to continue, especially such agencies as child health and development within the NIEHS system, but also the basic research and the applied research, developmental research that is conducted in the regulatory agencies as well.

A year ago, you reviewed the NTP program for this committee, and saw how it was getting off the ground. The NTP, I think, is emerging as a valuable resource for coordination and for assuring that certain types of testing needs are responded in a timely way with appropriate and reliable testing.

The idea behind the evolution of the NTP was to provide a loose confederation of agencies that would assist in carrying out this coordinative type of management. It operates under the guidance

of Dave Rall, who is the Director of NIEHS, but it is responsible to an executive committee that is composed of the leadership of the regulatory agencies, and the most approximately connected agencies within NIH with respect to research missions, such as the NCI.

And also, it has a very strong tie to CDC–NIOSH, as Dr. Millar has indicated.

The NTP also, in addition to this coordinative management function, has evolved what was recognized as the important need, namely, to have in hand a strategy for identifying those chemicals in the environment which needed to be tested, and a strategy criteria for ranking the priorities of those chemicals.

This has been accomplished on the basis of experience within EPA and other agencies, and recently in a study by the National Academy of Sciences has been published, and this described the achievement of its phase I study, which sets out to get a more general agreement, systematized, regularized, both the identification of need and the priority set of mechanisms.

NTP last year, as I recall, was described by Gilbert Ulman, who is one of the architects of this program, while he was in OMB, as the scientific research establishment that functions in harmony with regulatory needs. That is a good banner to fly under, and I hope we can achieve that.

The NTP has one of its principal elements, a carcinogenesis bioassay program. And one of the purposes in establishing the NTP was to broaden the assessment of health damage, toxicity, of compounds going into the bioassay by introducing other tests, such as reproductive function, short-term mutagenicity and neurochemical or neurobehavioral tests.

In great measure, that has been done. It is a complicated task; one that will take a long period of time. Let me turn, briefly, to the reproductive toxicology component of the NTP.

This is a cooperative program. It is sponsored by NIOSH, the National Center for Toxicological Research under FDA, and by NIEHS. I would describe the level of funding in that program as unrealistic to the aspirations, problems that have been set forth by previous witnesses here this morning.

Nevertheless, it represents a substantial beginning to a type of willingness by the participating agencies to pool their talents and develop coordinated testing needs and schedules for development of new programs.

That program functions as a loosely defined management scheme under the leadership of Dr. Kimmell from the NCTR, a well-recognized teratologist, reproductive biologist; the group is represented by one person from the NTP in our institute, Dr. Lamb, and Mr. Hardin from NIOSH.

The group has spent about 30 percent of its effort in developing new tests as well as conducting tests to meet the needs expressed through the priority mechanisms in the nominating committees.

That has been a productive and amiable relationship and I think is the kind of cooperative approach to these problems that we would like to see develop under the NTP.

NIEHS also sponsors in its other programs, particularly in its extramural grants programs and its intramural programs, a range of

reproductive toxicology research, some of it of a rather fundamental nature; some of it highly applied and programmatic.

We currently put a little bit more into our extramural programs than we do into our intramural programs. Within the intramural programs at NIEHS, we have two programs that are closely connected to the NTP and its mission.

On one side we have the biometry and risk assessment and epidemiology program, which is largely concerned with the evolution of statistical design, new test methods for evaluating outcomes in human population; and in particular has two projects dealing with reproductive toxicology.

One of them is a study of about 900 children in North Carolina to assess the possible correlation of PCBs in maternal breast milk with infant development. That is a study that is now through its early phases, but will take about another 4 or 5 years to complete.

It measures in breast milk and in the mother the levels of PCB's and tries to correlate this with outcomes in the developing infant.

There is another study that is under development, and it is just about ready to go, by Dr. Wilcox in the epidemiology group, which is attempting to design new ways to evaluate early reproductive loss in human populations.

One of the variables or outcomes that will be examined in this study is the evidence of pregnancy and pregnancy loss that may be based on assays of human chorionic gonadatropic hormones.

Another program is the intramural research program which we have one of our principal components represented by a reproductive group. In this group, we address problems that are of a more long-range nature; they are fundamental, but oriented toward environmental problems, and in this area, we emphasize assessments of fertility, transplacental carcinogenesis and teratology.

One of the main projects in the teratology program has been the evolution of a short-term so-called test system involving cell cultures of human embryo myxencomal cells from the palate.

And this is correlated with the production of cleft palate and is turning out to be a very successful, reliable bioasset. One interesting comment that I would like to make here: You can never tell where some of the information from the basic sciences is going to come that is applicable to problems of environmental health.

For instance, this test system was developed in the National Institute of Dental Research and we are continually being reminded that it is that undifferentiated base of biomedical science report which is so essential to sustain our ability to conduct these assessments, do these studies, that are deemed to be so important by your panelists who appeared here this morning.

In addition to these studies, let me say we place great emphasis in the extramural research program. We support centers in universities; we support individual investigator-initiated grants in universities; many of the elements I have described in our intramural programs are present in the extramural program.

It is a valuable source of information; it is the source, the principal source of training which everyone recognizes is a prominent need, and we are determined to sustain this level of funding.

The kind of work that is going on in our extramural programs range from epidemiological studies such as those conducted in Dr.

Selikoff's laboratory, which many of you are familiar with, to very basic studies in molecular genetics in many laboratories.

In just closing and recapitulating some idea about what we perceive to be research needs, I think that what has been said here this morning has been said very clearly, and I think that for the most part we would be quite supportive of the various particular points of view expressed.

I think that the need to support epidemiological studies in occupations must be viewed as a high priority. It is the opportunity, maybe in many circumstances, aside from tragic accidents, the only opportunity to study exposures with rather large amounts of chemicals in the environment.

Carefully designed studies, well-defined outcomes, modern methodology used into finding these outcomes is essential because, as the CEQ report emphasized over and over, many epidemiological studies are inconclusive, of poor design, contain inadequate data.

We also believe that, as Dr. Manson said this morning, there is a need to intensively look at how we can develop new indicators of outcome in human populations, such as the utility of human kinetotropic hormone assays to determine the incidence of early fetal loss.

We, and I think I share Art Bloom's concern about this, too, believe that a type of epidemiology that places great emphasis upon genetic factors is indispensable to the solution of many of these problems.

While I haven't described our programs in mutations and mutagenesity, frankly, we spend much more in that area than we do in reproductive toxicology.

And we do that, not because of reasons of fashion exclusively, but because we have much better defined evaluative techniques, and a much better defined science base on which to operate.

One area that I think will be surprising to all of us is the advances in molecular genetics, particularly recombinational DNA techniques, which make accessible new material from human populations that hitherto simply couldn't be worked with.

You can actually begin to do studies with human trophoblastic cells; you can clone genes and we, I think, as a federal government, as a nation, should certainly sustain the level of research in these areas. We look for this as a major outcome.

I think there are certain things that we can do that have been mentioned here. For one thing, in the face of some stringency in the way budgets are constructed these days, we can reprogram our funding to reflect some of these perceived and, I think, justifiably perceived needs.

We can continue to support, as we do, the environmental teratology register at Oak Ridge. The mutagenesis register; that is, the register of chemicals that cause mutations, at Oak Ridge is just as important to sustain, and we do that, too.

I believe that the way the expert witnesses have formulated this problem will help us and I think it is incumbent upon us to be responsive to many of the things that they highlight as needs.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Carter follows:]

STATEMENT OF CHARLES E. CARTER, M.D.

Mr. Chairman and Members of the Committee, I am pleased to appear before you today to discuss the research of the National Institute of Environmental Health Sciences (NIEHS) on the question of environmental chemical hazards to human reproduction. I am Charles E. Carter, Scientific Director of the Intramural Research Program, at NIEHS. My background is in biochemistry, pharmacology and in the scientific management of health effects research related to environmental chemical exposures.

NIEHS Programs

Before I begin let me briefly describe the mission of NIEHS. The Institute, one of the National Institutes of Health (NIH), supports and conducts research aimed at the development of knowledge basic to understanding of the processes by which human health can be adversely affected by the environment. To carry out this mission requires the involvement of a broad spectrum of disciplines and approaches. Work ranges from study of the very fundamental aspects of environmental health problems to more applied research associated with the detection of hazardous chemicals, the extrapolation of laboratory data to man and the estimation of human risk.

A year ago the structure and operation of the National Toxicology Program (NTP), which is administered by NIEHS, was reviewed before your Subcommittee. The aim of this program is to provide coordinated management of research and achieve a wider range of toxicological information in validated test systems. While providing this information through the testing of selected chemicals which are nominated by Federal agency members of its Executive Committee and others, the NTP also strives to develop new test systems that will provide critical information and assure that these systems are reliable. In its third year of existence, the NTP can demonstrate substantial progress toward these goals.

The development and application of these test systems for environmental toxicological problems at NIEHS are associated with two other research programs. The Biometry and Risk Assessment Program is concerned with epidemiological studies and with the methodology and estimation of risks related to environmental chemicals. The biological effects research in the Intramural Research Program asks how environmental chemicals cause damage to tissue and cells and how these effects are expressed--such as mutations, cancer and abnormal functions of pulmonary, neurological and reproductive systems. These studies are close to the basic biomedical research of other NIH Institutes but are oriented toward environmental health problems. This research aims to provide the fundamental information on which the detection and measurement of environmental hazards are based.

The NIEHS, through these programs, attempts to provide a continuum of research that engages in fundamental problems, the development of new toxicological test systems, the application of animal and cellular tests to environmental chemicals, and the incorporation of measurements from these and epidemiological studies into estimates of risk for human populations.

In the extramural programs sponsored by NIEHS there is representation of all of these research approaches. The research grants and research Centers' programs are situated in universities and represent investigator initiated research. Our support of extramural research exceeds that of intramural and we intend to sustain this relationship.

Research in Reproductive Toxicology and Epidemiology

Currently there are limited testing procedures available for assessing reproductive and developmental effects; those that are available provide only a crude indication of toxicity. The NTP addresses this need by placing emphasis on developing short-term tests in both reproductive toxicology and teratology, including *in vivo* and *in vitro* teratologic test systems and a continuous breeding assay for fertility assessment. Emphasis is also on using existing methodology to evaluate toxicity.

With the development of several new shorter term test procedures the NTP has been able to significantly increase the number of chemicals being evaluated. These abbreviated tests are being studied to determine their potential as screening devices.

In one case, this involves incorporation of reproductive endpoints into prechronic carcinogenesis and toxicology bioassays to obtain additional information on animals already being treated. This approach allows the testing of a much larger number of chemicals and priority-setting for more in-depth study of those chemicals which appear to present a significant risk for human exposure. This more efficient utilization of resources will eventually provide the ability to address questions about the magnitude of problems in reproductive and developmental toxicology and about mechanisms of action.

The NTP work in this area is carried out and closely coordinated with scientists at the National Institute for Occupational Safety and Health (NIOSH)/Centers for Disease Control and the National Center for Toxicological Research (NCTR)/Food and Drug Administration as well as by NIEHS scientists. NIEHS supports much of the work at NIOSH and NCTR through interagency agreements.

Within the NIEHS component of NTP studies are underway which involve both integrated and short-term testing systems. The chemicals selected for testing are generally ones which have already been tested in a multigeneration assay. A protocol which has the potential of providing data comparable to the multigeneration assay at a fraction of the cost has been designed. This system is being compared to the existing data from multigeneration assays and the data from the two testing laboratories are being directly compared to each other at the same time. We should be able to detect the effect of a low-level chemical exposure on the number of fertile matings, litter size, offspring survival and even evaluate perinatal influences or study target organ reponses in the affected animals. The time required is only about half that for a multigeneration assay.

NIEHS/NTP has also begun incorporating specific reproductive endpoints into the prechronic phase of the carcinogenesis and toxicology bioassay. This allows us to study the influence of chemical exposure on sperm number, sperm motility, and sperm morphology in male rats and mice and on the reproductive cycle in female rats and mice. These studies can be done without treating any additional animals in the prechronic study, thus making more efficient use of the animals and chemicals on test in the bioassay.

In-house NIEHS/NTP research efforts include investigations into the influence of certain reproductive toxicants including 1,2 dibromo-3-chloropropane (DBCP) and chlordecone (Kepone) on target organs. These investigations are employing state of the art methods in reproductive biology. The goal of these studies is to evaluate the effects and mechanisms of toxicity of selected chemicals. As the testing efforts are established we expect that the testing systems will lead us to new and important chemicals that will be studied in depth. These investigations have employed morphological, biochemical and in vitro methods.

Other research into the relationship between chemicals and reproductive function is conducted intramurally in NIEHS' Laboratory of Reproducitve and Developmental Toxicology. This research effort is unique because it involves both basic and applied studies which bridge the gap between the most molecular aspects of reproductive biology and endocrinology and the more applied problems associated with the estimation of health risk.

Scientists in this laboratory direct their efforts to three major areas: male and female reproductive processes, teratogenesis, and postnatal effects of gestational chemical exposure.

Some significant research advances have developed in this laboratory. An animal model has been developed which closely approximates the reproductive tract abnormalities, including cancer, seen in young men and women exposed prenatally to diethylstilbestrol (DES). It is being used to study the further development of tumors and reproductive problems in this population as well as to assess the potential of other estrogenic environmental chemicals to produce similar toxicity.

Scientists are studying the Fetal Alcohol Syndrome, a very common, chemically-induced birth defect. Studies are in progress in cell and whole embryo-culture to examine the biochemical basis for fetal sensitivity to ethanol. Efforts are also being made to understand how chemicals cause birth defects, such as cleft palate, and to identify individuals who might be particularly susceptible. A "teratogenic index" has been introduced by staff scientists. This is a conceptual appproach which improves ability to select from among the many laboratory teratogens those chemicals with the greatest potential to harm the developing human.

Two investigators have been studying the molecular basis of both benign and malignant prostatic disease and the role of environmental chemicals in the etiology of these health effects so common among aging men. Other scientists have contributed to our understanding of the role of chemical activation and the blood-testis barrier in determining which chemicals damage the testis. They are also using monoclonal antibodies to identify changes in sperm surface proteins which are induced by chemicals and can be associated with dysfunction.

NIEHS' Biometry and Risk Assessment Program is involved in both epidemiological and statistical work related to the issue of chemical effects on reproduction. Work in reproductive epidemiology emphasizes the developement of new methods for measuring and analyzing human reproductive outcomes. This includes fertility, sub-clinical early fetal loss, spontaneous abortion, fetal growth and infant birth weight. Each of these outcomes may be affected by environmental factors and represents a likely endpoint for studying the effects of toxic substances on human reproduction. A study of the validity of measuring spontaneous abortion by interview is being conducted. There is also a study of laboratory methods for very early pregnancy detection and fetal loss being planned.

A major ongoing field investigation is the Breast Milk and Formula Project, a prospective, birth cohort study of about 900 North Carolina children. Clinical data on growth, morbidity, and development are gathered on the children; levels

of widespread contaminant chemicals, such as PCBs (polychlorinated biphenyls) and DDE (the stored metabolite of DDT) are measured in the mother at birth and in breast milk over time. Enrollment of children has been completed; a substantial number of the cohort is now two to three years old; most of the chemical analyses are complete, and data analysis has begun. The very high prevalence of breast milk contaminated with these chemicals (more than 90 %) has been confirmed; and data on the association between duration of breast feeding and contaminant level has been evaluted. This long term study is expected to aid in the development of methodology for screening human populations for chemical exposure and in measuring and understanding early developmental effects.

In statistics this program is developing methodology useful in assessment of human health risk associated with exposure to hazardous environmental agents. Studies of the factors which influence species variability for non-carcinogenic endpoints such as teratogenic effects are underway. There is also work on development of improved statistical techniques for analysis of various kinds of epidemiological studies. Preliminary work is being done on the effectiveness of various matching schemes in the study of spontaneous abortions.

Through its Extramural Program NIEHS supports a substantial amount of university based research in reproductive toxicology. The preponderance of projects are looking at the implications for offspring of maternal exposure to hazardous substances.

Various heavy metals are being studied for their neurotoxic effects on the developing nervous sytem. Emphasis is placed on utilizing those animal and in vitro models which most directly allow testing of the hypothesis that the developing nervous system is more sensitive than the mature system to metals such as methyl mercury, lead and aluminum.

Other research projects are examining the effects of prenatal exposure in utero to low levels of pesticides. Various levels of Kepone exposure are being studied for their effect on
reproductive capability and to determine whether testicular damage can be reversed after exposure is discontinued.

Currently we are supporting an animal study to examine the potential of low levels of polybrominated biphenyls (PBBs) to induce lasting change in behavior. An earlier study of children exposed to PBB indicated they may show subtle disturbances in learning patterns, but conclusive evidence of perinatal toxicity in humans has not yet been

demonstrated. Another recent study demonstrated perinatal toxicity in rats exposed to large doses. The study being funded is attempting to define the lowest dose level of PBB exposure which affects behavior patterns. Research on polychlorinated biphenyls (PCBs) is also being supported. One study in particular is looking at the effect that various doses fed to lactating rats have on offspring reproductive ability, mating behavior, and activity and learning when they reach adulthood. There is particular interest in determining if any effects are apparent immediately upon reaching maturity or if the effects are delayed.

As a result of the widely ranging research NIEHS is conducting and supporting we hope to develop answers to some very fundamental questions about the relationship between environmental factors and human reproduction.

Issues Raised in CEQ Report

The report by the Council on Environmental Quality (CEQ) on "Chemical Hazards to Human Reproduction" touches on several of the major difficulties which currently exist in reproductive toxicology and epidemiology. As the report implies the problem is not well defined; because of the uncertainties cited it is impossible to know its full magnitude. Current laboratory approaches, for the most part, are not reliably predictive and many studies in human populations are inconclusive. There are, in fact, only about a dozen environmental (including occupational) chemicals which are known to affect human reproduction.

The emphasis placed by the authors of the CEQ report and others on the need for more research to improve short-term screening tests is understandable. Yet, if the status of reproductive toxicology is to be compared with carcinogenesis testing twenty years ago there is a lesson to be gained. The short-term testing systems in mutagenesis have made tremendous contributions to our understanding of the mechanisms of carcinogenesis and the estimation of carcinogenic potential. Also, we have learned that there is no short cut to evaluating chemical carcinogenesis in chronic animal testing. Reproductive toxicology, like carcinogenesis, involves the study of complicated and integrated systems. We would be remiss were we to overstate the potential of short-term screening tests to replace long-term animal testing systems.

Research Needs

For over a hundred years it has been known that high concentrations of lead in occupational exposures caused reproductive damage in humans. Twenty years ago thalidomide was

identified as the cause of severe congenital malformations among children whose mothers had taken the sedative during pregnancy. Dr. Joshua Lederberg has speculated that if thalidomide had caused a 20 decrease in I.Q., rather than gross and unusual abnormalities, it might now be on the market.

In your letter, Mr. Chairman, you asked that I comment on research needs in this area of public health concern. As prelude to my comments I want to emphasize that over the last two decades there have been important scientific developments in a variety of areas bearing on these problems:

-- Greatly increased understanding of basic biological and behavioral mechanisms underlying reproduction and development.

-- Expanded understanding of the potential for health hazard posed by some chemicals and classes of chemicals.

-- Significant developments in our understanding of the basic mechanisms of action of a variety of substances to which we are exposed.

Development in each of these areas have resulted in the identification of more questions. To answer these we need to develop:

-- Improved capability for surveillance of occupational and other exposed populations.

-- A clearer picture of the basic genetic, molecular and endocrine factors involved in the very early stages of fertilization and embryonic development.

-- An improved understanding of the biological processes which chemical insults can trigger in the reproductive and developmental system.

-- Improved epidemiological techniques for identifying causes for the rather large proportion of fetal malformations for which we have little or no explanation.

-- Better understanding of the role of confounding factors such as tobacco, alcohol, nutrition, socioeconomic status and access to medical care.

Beyond this however, we also need to enhance the ability to integrate our knowledge in this area so that we can build both a conceptual and practical framework within which our answers can be placed. My view is that the real surge in knowledge about reproductive problems may come in developmental molecular genetics, an area requiring research on some fundamental issues, but holding enormous potential for developing the explanations required for a reliably predictive experimental toxicology.

This concludes my testimony. I would be glad to answer any questions you may have.

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Scientific Director (NIEHS)

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Mr. GORE. Thank you very much, Dr. Carter.

The Office of Science and Technology Policy set up an interagency panel to develop guidelines for determining carcinogenic potential of exposure to certain chemicals.

What would you think of a similar effort with respect to human reproduction hazards?

Dr. CARTER. Do you want me to answer?

Mr. GORE. Both of you. Briefly.

Dr. CARTER. I think that only benefit could come from it.

Mr. GORE. Dr. Millar?

Dr. MILLAR. I would agree.

Mr. GORE. OK, we may recommend that in our report, but let's think about it.

I want to ask you about some specific chemicals. Dr. Millar, what is the quality of the data associating reproductive hazards with exposure to anesthetic gases, first of all?

Dr. MILLAR. Well, we have felt the quality sufficient to issue a criteria document on it in 1977. I think that what you heard this morning represents a good view of—at least our view, of the current situation: There is some evidence of fetal wastage in workers exposed to waste anesthetic gases, but I don't think we have a definition of the problem with regard to specific agents that would be useful.

Mr. GORE. Now, when you say fetal wastage, you mean——

Dr. MILLAR. Abortion.

Mr. GORE. Woman losing——

Dr. MILLAR. That is right. Spontaneous abortion.

Mr. GORE. What about impairments or deformities? Is it just simply abortions?

Dr. MILLAR. Well, as far as I know personally, the data that you heard this morning, the interpretation that you heard this morning suggests that there is a lower level of association between exposure and deformities than between exposures and fetal wastage.

Mr. GORE. And NIOSH has recommended a standard for the anesthetic gases?

Dr. MILLAR. We have a criteria document on it which was sent to OSHA in 1977. I am sorry I can't tell you what the recommended permissible level is.

Mr. GORE. I believe 25 parts per million, is the recommended level.

Dr. MILLAR. Thank you.

Mr. GORE. Now, with respect to ethylene oxide, what is the quality of the data associating reproductive hazards with ethylene oxide?

Dr. MILLAR. Well, we feel like that it is a demonstrated animal mutagen and carcinogen and we are currently attempting to initiate a feasibility study in hospital supply personnel, hopefully to shed some light on the human findings.

And as you heard already, sister-chromatid exchange [SCE] has been observed, I would say that here again, there are good animal data, but the human data are not clear.

Mr. GORE. Now, there is a current OSHA exposure level for ethylene oxide of 50 parts per million; is that accurate?

Dr. MILLAR. I will take your word for it.

Mr. GORE. All right.

Have you made additional recommendations to OSHA with respect to ethylene oxide?

Dr. MILLAR. I don't believe we have made any recently; certainly not since I have been Director.

Mr. GORE. All right.

Now, asking about another specific instance, what effort has NIOSH made to study the rate of birth defects at the Eli Lilly Rensselaer, N.Y., plant?

Dr. MILLAR. Well, I am told that we have, indeed, done some investigations there, and have, I believe, confirmed five abnormal outcomes of pregnancy, including three that involved heart defects.

This was work done by one of our assignees in the New York State Health Department, as I understand it.

Mr. GORE. What is the preliminary assessment of the study by NIOSH?

Dr. MILLAR. Well, I don't—you mean whether it is good, bad or indifferent?

Mr. GORE. Well, it doesn't sound good, but yes.

Dr. MILLAR. I think we conclude that this is an interesting finding that needs further development.

Mr. GORE. When do you anticipate having concrete results from your review of the data?

Dr. MILLAR. I can't tell you that, but I would be happy to supply it.

Mr. GORE. Has NIOSH relied upon any reports or information prepared by the Eli Lilly Co.?

Dr. MILLAR. I don't know the answer to that.

Mr. GORE. Has NIOSH been supplied with any such reports by EPA?

Dr. MILLAR. I don't know the answer to that.

Mr. GORE. Do any of your colleagues here with you know the responses to these questions?

Somebody—is that one of your staff, Dr. Millar, in the back—could you identify yourself to the reporter? Please come forward to the witness table, if you would.

Mr. ROSENBERG. My name is Michael Rosenberg, I am Chief of Reproductive Health Activity, which is the epidemiologic activity within NIOSH that deals with reproduction.

Let me step back a moment and just say that at this plant, there was an insecticide manufactured, and the union became concerned because there were five birth outcomes which they considered abnormal.

As Dr. Millar mentioned, there were three cardiac abnormalities; there was another child that died of pneumonia; and the fifth outcome was a spontaneous abortion.

We are in the process of looking at that question with information that is being supplied to us by the State of New York, which keeps records of all spontaneous abortions that occur in the State, as well as malformations.

We have gotten background information from Lilly and from the EPA. They are both in the form of animal studies.

Mr. GORE. Have you kept track of EPA's efforts concerning the pesticide in question; it is Oryzalin, is that correct?

Mr. ROSENBERG. That is correct.

Mr. GORE. It is a pesticide and a herbicide, right?

Mr. ROSENBERG. That is right.

Mr. GORE. Have you kept track of EPA's efforts concerning Oryzalin?

Mr. ROSENBERG. I have not. There is another of my staff who is working on that, and I think he is keeping track of that.

Mr. GORE. How would you view EPA's apparent conclusion that the birth defect rate at this plant among employees at the plant is "not unusual?"

Mr. ROSENBERG. Well, I think I would have to disagree with that statement. I think there is clearly something unusual going on, but the question is whether what is unusual can be attributed to the exposure to Oryzalin. And I think that question is not answered right now.

Mr. GORE. We have a vote on the floor, and could we submit some additional questions to you all for the record? If so, then I would like to thank you for your appearance here today. Thank you very much, and we have three more witnesses making up our final panel. With their indulgence and the indulgence of our guests, we are going to adjourn for approximately 10 minutes for the vote on the floor, and then we will come back.

[Recess.]

Mr. GORE. The subcommittee will come back to order. I apologize for the delay.

Our third panel is made up of Dr. F. Gordon Hueter, Director of the Health Effects Laboratory for the Environmental Protection

Agency; Dr. Leonard Vance, Director of Health Standards, with OSHA; and Dr. Gary Flamm, Acting Associate Director for Toxicological Substances with the Bureau of Foods at the Food and Drug Administration.

Gentlemen, if all three of you would come to the witness table, we are glad to have you here. And without objection, the prepared statements you have submitted will be included in the record in full, and we invite you to proceed at this time, beginning with Dr. Gordon Hueter.

STATEMENTS OF DR. F. GORDON HUETER, PH. D., DIRECTOR, HEALTH EFFECTS LABORATORY, ENVIRONMENTAL PROTECTION AGENCY, RESEARCH TRIANGLE PARK, N.C., ACCOMPANIED BY ED JOHNSON, DIRECTOR, OFFICE OF PESTICIDE PROGRAMS; LEONARD VANCE, M.D., DIRECTOR OF HEALTH STANDARDS, OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION, DEPARTMENT OF LABOR, WASHINGTON, D.C., ACCOMPANIED BY ROBERT P. BELILES, DIRECTOR, OFFICE OF CARCINOGEN STANDARD HEALTH STANDARDS PROGRAM, OSHA; AND GARY FLAMM, M.D., ACTING ASSOCIATE DIRECTOR FOR TOXICOLOGICAL SUBSTANCES, BUREAU OF FOODS, FOOD AND DRUG ADMINISTRATION, WASHINGTON, D.C.

Dr. HUETER. Good afternoon, Mr. Chairman and members of the subcommittee. I am Gordon Hueter, Director of the U.S. Environmental Protection Agency's Health Effects Research Laboratory at Research Triangle Park.

I welcome this opportunity to meet with you and the other members of the panel to discuss research on the hazards of chemicals to human reproduction.

Mr. Edwin L. Johnson, Director of the Office of Pesticide Programs, and Dr. Richard N. Hill, who is Senior Science Adviser to EPA's Assistant Administrator for Pesticides and Toxic Substances, are with me today. These gentlemen will be able to address the translation of the research information into regulatory decisionmaking.

The Environmental Protection Agency is aware of the potential of environmental agents to affect adversely the reproductive capability and/or the development of the human conceptus. There have been instances in both the environment and in the workplace—for example, the methylmercury-induced birth defects in Japan, previously mentioned, DBCP and kepone-induced sterility in men—which alerted the research community as a whole to the need for adequate human population monitoring and animal testing of compounds.

Research in this area has not been centered in any one agency or group, but rather has been shared by numerous Government agencies including the National Center for Toxicological Research, National Institute for Environmental Health Sciences, National Toxicology Program, National Institute for Occupational Safety and Health, Food and Drug Administration, Department of Energy, EPA, and others.

At the laboratory level, we are in communication with all of these organizations, having joint workshops and performing collaborative research.

In addition, various governmental groups in other countries as well as numerous scientists in academic institutions are also engaged in such research.

Further, under some statutes, the producing industry bears a heavy research burden; for instance, regulatory actions on pesticides are based to a large extent on studies required by the Agency but performed by the regulated industry.

The reproductive and developmental processes of mammals are extremely complex and their success depends upon a myriad of interrelated morphological, physiological, and biochemical events.

This complexity raises serious questions as to whether these processes may be especially sensitive to environmental insults, particularly concerning the examples mentioned previously.

In considering reproductive failure in relation to environmental exposures, we often define reproductive failure as an increase in one or more of a list of undesirable endpoints. Many endpoints are not independent, and an increase in one deleterious endpoint may be the result of a change in another. For example, neonatal mortality rates may increase as the late fetal death rate decreases. Endpoints which have been used may cover a broad list of topics: sexual dysfunction, sperm abnormalities, lowered fecundity, illness during pregnancy and parturition, early fetal loss, perinatal death, altered sex ratios, birth defects, chromosomal abnormalities, early death in the offspring, or other ill effects in the offspring.

In assessing human risks from exposure to potentially toxic chemicals, many considerations should be addressed, such as severity, reversibility or irreversibility of the effect, the existence of threshold or nonthreshold levels, dose-response relationships, sensitivity of the toxicological response evaluated, and predictive ability of animal studies to determine the risk to humans.

In developing a research program, we must ask ourselves, "What are the most relevant questions to work on?" and "Are these questions ripe for research?" Because EPA is a regulatory agency which must make decisions on the relative costs and benefits of various levels of pollutants in the environment, the relevant questions for EPA to answer are those which will make quantitative reproductive risk assessments possible.

This year, the Environmental Protection Agency published the report, "Assessment of Risks to Human Reproduction and to the Development of the Human Conceptus From Exposure to Environmental Substances." This report is based on a workshop on how to do risk assessments for teratogenesis, male infertility, and female infertility. The workshop's participants were nationally and internationally known scientists from academia, industry, and government. This effort provides a first step for developing reproductive risk assessment guidelines and also identifies specific areas where research is needed.

From a regulatory standpoint, there is a two-part assessment process for the evaluation of chemicals that may pose a reproductive hazard to humans. The first is a qualitative evaluation of in-

formation bearing on a chemical's ability to induce in humans or experimental animals an adverse reproductive outcome.

If an agent is judged to have the potential for reproductive impairment, a quantitative evaluation of the degree of hazard associated with exposures is undertaken.

Because of the lack of appropriate information on humans, one must usually rely on the results of experimental animal testing.

The quantitative assessment usually requires knowledge of two items: The highest dose in experimental animals that is not associated with an adverse reproductive outcome—called the no-observed-effect level, or NOEL, acronym—and the expected human exposure.

It is generally agreed that for most reproductive endpoints the degree of safety associated with any measured or estimated human exposure level is expressed as a ratio of the NOEL to the human exposure. The larger the value of the ratio, the greater the confidence the human exposure level may be of little concern.

Most scientific bodies claim that ratios in excess of 1,000 to 2,000 are probably of little concern. As the ratio moves in the other direction, below 100 and toward unity or less, concern increases accordingly.

The judgment as to what ratio constitutes a "safe enough" level and what may require some regulatory intervention is difficult to make. It requires evaluation of all the scientific information as well as the Federal act and the requirements it places on the decisionmakers.

For instance, some acts at EPA are technology-based, for example, parts of the Clean Air Act, that require administrators to look at the technological feasibility of control.

Still others, like the Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act, are risk-benefit statutes that require a balancing of both the risk factors as well as the economic consequences of regulation.

Regulators must make a number of judgments in the face of scientific uncertainty. Is the chemical in question likely to cause adverse reproductive effects in humans, when the only existing information comes from experimental animals? And if it is concluded that an agent may pose a risk to humans, what levels of human exposure may be problematic? A third uncertainty deals with the innate limitations of any experimental animal test system. The existing ones in common use measure only certain reproductive endpoints like general reproductive success as measured by the proportion of females pregnant, the number of live pups born per litter and the incidence of structural congenital malformations. Last, we have little understanding of the mechanisms by which toxic insults are generated. Additional research is required.

An example of a case in which we had particularly strong evidence of adverse reproductive and other serious health effects which provided a basis for a strong regulatory action is the pesticide, DBCP, dibromochloropropane.

In this case, we had animal data which showed that the chemical had potential for causing sterility and cancer. In addition, there was evidence that a significant number of male workers in plants

producing the pesticide had abnormally low sperm counts and sterility.

EPA, OSHA, and FDA acted collectively to curtail immediately human exposure to the pesticide; EPA suspended the pesticide registration, which is the strongest immediate action we are empowered to take under the pesticide law, and later canceled virtually all registrations.

Obviously, strength of the regulatory response must be based on the strength of the evidence. DBCP is not the usual case, since we had both animal data and demonstrable human effects.

To establish a better scientific foundation for reproductive risk assessment, a vigorous research program is underway. The building blocks for this foundation comes from studies to generate data on the reproductive effects of agents; the development of animal and in vitro methods which can be used to generate data on the reproductive effects of agents; and the development of methods to use data from such studies to predict risk to human populations.

In response to these needs, the Environmental Protection Agency conducts research on the reproductive effects of particular agents of concern to the Agency, including pesticides, toxic substances, air pollutants, water pollutants, and non-ionizing radiation. The biological parameters studied, in the appropriate animal species, include teratogenesis, postnatal alterations of organ function, reproductive physiology and the histopathological correlates of the above, or the preceding.

We also develop new and improved methodologies for the assessment of prenatal dysfunction and reproductive impairment. Existing methods are studied and improvements in the types of data generated as well as the interpretation of such data are sought. The reproductive parameters studied include gonadal and accessory gland development, hypothalamic-pituitary integrity, reproductive hormone profiles, germ cell morphology and viability, and reproductive behavior.

We also conduct studies to improve extrapolation from high dose to low dose and from animals to man. To help do this we are investigating the influence of critical periods of susceptibility to chemicals during laboratory animal development and dose-response relationships of reproductive toxicants in pituitary and germinal cell cultures from several species.

The Environmental Protection Agency has been doing research on the reproductive effects of environmental agents since the early 1970's. Since that time, we have assembled a staff of scientists engaged in research on reproductive toxicology and teratology to form the Developmental Biology Division of the Health Effects Research Laboratory, and we have established the Reproductive Effects Assessment Group which develops Agency-wide guidelines for assessing reproductive effects and performs some of these assessments.

We work with other institutions in the Federal sector, and fund competitively awarded grants for exploratory research in the reproductive area.

We have increased the resources in our program for reproductive effects from under $2 million in fiscal year 1978 to more than $3

million in the fiscal year 1983 President's budget, for a total program of $17 million over those 6 years.

I also would like to add I have in the audience, Dr. Neil Chernoff, who is the Director for the Developmental Biology Division of the Health Effects Laboratory in Research Triangle Park.

Dr. Chernoff is certainly more expert in these matters than I.

Thank you, Mr. Chairman, that concludes my statement.

[The prepared statement of Dr. Hueter follows:]

STATEMENT OF DR. F. GORDON HUETER

Good morning, Mr. Chairman and Members of the Subcommittee. I am Gordon Hueter, Director of the U.S. Environmental Protection Agency's (EPA) Health Effects Research Laboratory at Research Triangle Park. I welcome this opportunity to meet with you and the other members of the panel to discuss research on the hazards of chemicals to human reproduction. Mr. Edwin L. Johnson, Director of the Office of Pesticide Programs and Dr. Richard N. Hill, Senior Science advisor to EPA's Assistant Administrator for Pesticides and Toxic Substances, are with me today. These gentlemen will be able to address the translation of research information into regulatory decision-making.

The Environmental Protection Agency is aware of the potential of environmental agents to affect adversely the reproductive capability and/or the development of the human conceptus. There have been incidents in both the environment and in the workplace (e.g., methylmercury-induced birth defects in Japan, DBCP and kepone-induced sterility in men), which alerted the research community as a whole to the need for adequate human population monitoring and animal testing of compounds. Research in this area has not been centered in any one Agency or group, but rather has been shared by numerous government agencies including the National Center for Toxicological Research, National Institutes for Environmental Health Sciences, National Toxicology Program, National Institute for Occupational Safety and Health, Food and Drug Administration, Department of Energy, EPA, and others. At the laboratory level we are in communication with all of these organizations, having joint workshops and performing collaborative research. In addition, various governmental agencies in other countries as well as numerous scientists in academic institutions are also engaged in such research. Further, under some statutes, the producing industry bears a heavy research burden; for instance, regulatory actions on pesticides are based to a large extent on studies required by the Agency but performed by the regulated industry.

The reproductive and developmental processes of mammals are extremely complex and their success depends upon a myriad of interrelated morphological, physiological, and/or biochemical events. This compelxity raises serious questions as to whether these processes may be especially sensitive to environmental insults, particularly considering the examples I mentioned previously. In considering reproductive failure in relation to environmental exposures, we often define reproductive failure as an increase in one or more of a list of undesirable endpoints. Many endpoints are not independent, and an increase in one deleterious endpoint may be the result of a change in another. For example, neonatal mortality rates may increase as the late fetal death rate decreases. Endpoints which have been used may cover a broad list of topics: sexual dysfunction, sperm abnormalities, lowered fecundity, illness during pregnancy and parturition, early fetal loss, perinatal death, altered sex ratios, birth defects, chromosomal abnormalities, early death in the offspring, or other ill-effects in the offspring. In assessing human risks from exposure to potentially toxic chemicals, many considerations should be addressed, such as severity, reversibility or irreversibility of the effect, existence of threshold or non-threshold levels, dose-response relationships, sensitivity of the toxicological response evaluated, and predictive ability of animal studies to determine the risk to humans.

In developing a research program, we must ask ourselves, "What are the most relevant questions to work on?" and "Are these questions ripe for research?" Because EPA is a regulatory agency which must make decisions on the relative costs and benefits of various levels of pollutants in the environment, the relevant questions for EPA to answer are those which will make quantitative reproductive risk assessments possible.

This year the Environmental Protection Agency published the report, "Assessment of Risks to Human Reproduction and to the Development of the Human Conceptus from Exposure to Environmental Substances." This report is based on a

workshop on how to do risk assessments for teratogenesis, male infertility, and female infertility. The workshop participants were nationally and internationally known scientists from academia, industry, and government. This effort provides a first step for developing reproductive risk assessment guidelines and also identifies specific areass where research is needed.

From a regulatory standpoint there is a two-part assessment process for the evaluation of chemicals that may pose a reproductive hazard to humans. The first is a qualitative evaluation of information bearing on a chemical's ability to induce in humans or experimental animals an adverse reproductive outcome. If an agent is judged to have the potential for reproductive impairment, a quantitative evaluation of the degree of hazard associated with exposures is undertaken. Because of the lack of appropriate information on humans, one must usually rely on the results of experimental animal testing.

The quantitative assessment usually requires knowledge of two items: the highest dose in experimental animals that is not associated with an adverse reproductive outcome (called the no-observed-effect level or NOEL) and the expected human exposure. It is generally agreed that for most reproductive endpoints the degree of safety associated with any measured or estimated human exposure level is expressed as a ratio of the NOEL to the human exposure. The larger the value of the ratio, the greater the confidence the human exposure level may be of little concern. Most scientific bodies claim that ratios in excess of 1000 to 2000 are probably of little concern. As the ratio moves in the other direction, below 100 and toward unity or less, concern increases accordingly. The judgment as to what ratio constitutes a "safe enough" level and what may require same regulatory intervention is difficult to make. It requires evaluation of all the scientific information as well as the Federal Act and the requirements it places on the decisionmakers. For instance, some acts at EPA are technology-based, e.g., parts of the Clean Air Act, that require administrators to look at that technological feasibility of control. Still others, like the Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act, are risk-benefit statutes that require a balancig of both the risk factors as well as the economic consequences of regulation.

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To establish a better scientific foundation for reproductive risk assessment, a vigorous research program is underway. The building blocks for this foundaton comes from (1) studies to generate data on the reproductive effects of agents; (2) development of animal and in vitro methods which can be used to generate data on the reproductive effects of agents and (3) development of methods to use data from such studies to predict risk to human populations.

In response to these needs, the Environmental Protection Agency:

1. Conducts research on the reproductive effects of particular agents of concern to the Agency, including pesticides, toxic substances, air pollutants, water pollutants, and non-ionizing radiation. The biological parameters studied, in the appropriate animal species, include teratorgenesis, postnatal alterations of organ function, reproductive physiology, and the histopathological correlates of the above.

2. Develops new and improved methodologies for the assessment of perinatal dysfunction and reproductive impairment. Existing methods are studied and improve-

ments in the types of data generated as well as the interpretation of such data are sought. The reproductive parameters studied include gonadal and accessory gland development, hypothalamic-pituitary integrity, reproductive hormone profiles, germ cell morphology and viability, and reproductive behavior.

3. Conducts studies to improve extrapolation from highi dose to low dose and from animals to man. To help do this we are investigating the influence of critical periods of susceptibility to chemicals during laboratory animal development and does-response relationships of reproductive toxicants in pituitary and germinal cell cultures from several species.

The Environmental Protection Agency has been doing research on the reproductive effects of environmental agents since the early 1970's. Since that time we have assembled a staff of scientists engaged in research on reproductive toxicology and teratology to form the Developmental Biology Division of the Health Effects Research Laboratory, and we have established the Reproductive Effects Assessment Group which develops Agency-wide guidelines for assessing reproductive effects and performs some of them. We work with other institutions in the Federal sector, and fund competitively awarded grants for exploratory research in the reproductive area. We have increased the resources in our program for reproductive effects from under $2M in fiscal year 1978 to more than $3M in the fiscal year 1983 President's budget, for a total program of $17M over those six years.

Thank you, Mr. Chairman. That concludes my statement.

Mr. GORE. Thank you very much.

We will hear now from Dr. Leonard Vance, Director of Health Standards, with the Occupational Safety and Health Administration. Welcome, Dr. Vance.

Dr. VANCE. Thank you, Mr. Chairman. We appreciate your inviting me here today to participate in the subcommittee's hearing on possible hazards to human reproduction.

I am Leonard Vance, Director of Health Standards Programs for the Occupational Safety and Health Administration.

OSHA shares the general concern about reproductive hazards and welcomes the subcommittee's interest in this subject. As the Federal agency with primary regulatory responsibility for workplace safety and health, OSHA must deal with all job-related hazards, including those which affect human reproduction.

As a regulatory agency, before OSHA can promulgate any permanent health standard, the Secretary of Labor is required to make two determinations: First, that a place of employment is unsafe in the sense that a significant risk to workers is present and, second, that this risk can be eliminated or lessened by the promulgation of a standard or a change in an existing standard.

Since OSHA does not conduct its own research, we must rely on the scientific community to provide the information OSHA needs in order to have standards. At this time, in OSHA's judgment, the scientific evidence does not support the adoption of a generic type of policy or standard for reproductive hazards.

The recent report, "Chemical Hazards to Human Reproduction," supports this judgment. This report was prepared, as you know, Mr. Chairman, by Clement Associates for the Council on Environmental Quality with funding from NIOSH, from EPA, and from OSHA.

The report failed to establish a scientific foundation for a general OSHA regulatory policy for reproductive hazards.

There is information to the effect that some specific agents found in the workplace impair sexual functions and the ability to reproduce healthy offspring. Few studies have been conducted, however,

of the potential effect on human reproduction of the great majority of potentially toxic materials in the workplace.

Additionally, as noted in the CEQ report, dangers and potential dangers to the human reproductive system can come from a wide variety of sources unrelated to working conditions.

For instance, poor maternal health, inadequate diet, the use of tobacco and alcohol, and the possible effects of chemical exposures in the environment and in the home, as well as in the workplace, all have the potential for affecting human reproduction.

This multicausal nature of reproductive toxicity makes it exceedingly difficult to attribute a particular share of the problem to any one of these factors. The reports note that it is "fairly difficult" to identify reproductive hazards for occupational exposures to hazardous chemicals and "very difficult" for general environmental exposures.

Thus, the state of awareness of the occupational setting as a factor in the etiology of human reproductive impairment is limited and does not permit sufficient generalizations about the nature and extent of reproductive effects on which to base regulation, other than on a case-by-case basis. And on a case-by-case basis is how we do it at this time.

Lack of information, then, makes it impossible for OSHA to address workplace reproductive hazards as a generic issue. The agency has to deal with such hazards on a case-by-case basis.

Thus, OSHA considers reproductive hazards as part of the total picture of hazards to human health. In the past, OSHA has responded to protect employees when appropriate and will continue to do so.

For example, in its standard for occupational exposure to lead, in addition to other hygiene measures, OSHA requires that exposed employees must be trained and counseled on the dangers of lead to their reproductive systems.

Similarly, information about sterility in male workers was a factor in OSHA's decision to regulate the nematocide, DBCP, dibromochloropropane. More recently, in Advance Notices of Proposed Rulemaking on ethylene oxide and ethylene dibromide, OSHA refers to studies showing that both of these chemicals are mutagens or teratogens in experimental animals.

Another recent demonstration of OSHA's concern for potential reproductive hazards in its rulemaking on health standards is the trade secrets protection provisions of the hazard communication standard published in March of this year.

OSHA has proposed to prohibit chemical manufacturers from the blanket withholding of the chemical name of a substance that is a carcinogen, mutagen or teratogen on the grounds that proprietary information would be divulged.

This proposed prohibition would apply even when a chemical manufacturer clearly demonstrates the trade secret value of the chemical name of a substance.

In this same hazard communication proposal, OSHA has also expressly included reproductive toxins in the list of health hazards of particular concern.

In addition, in the area of training and education, OSHA has provided grants to projects in which nonprofit organizations pro-

vide information for workers on the potential hazards of chemical exposures to the reproductive system.

In summary, OSHA, as a regulatory agency can act only on the basis of scientific knowledge, and for that knowledge, it must rely on the scientific community. OSHA is closely following the progress of research in this area and will continue to consider the scientific evidence on reproductive hazards as part of its general health standards activities.

Thank you, Mr. Chairman. I will be happy to attempt to answer any questions the Chair might have.

[The prepared statement of Dr. Vance follows:]

STATEMENT OF DR. R. LEONARD VANCE

Mr. Chairman and Members of the Subcommittee, thank you for inviting me here today to participate in the Subcommittee's hearing on possible hazards to human reproduction. I am Leonard Vance, Director of Health Standards Programs for the Occupational Safety and Health Administration (OSHA).

OSHA shares the general concern about reproductive hazards and welcomes the Subcommittee's interest in this subject. As the federal agency with primary regulatory responsibility for workplace safety and health, OSHA must deal with all job-related hazards, including those which may affect human reproduction.

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There is information to the effect that some agents found in the workplace may impair sexual functions and the ability to produce healthy offspring. Few studies have been conducted, however, of the potential effect on human reproduction of the great majority of potentially toxic materials in the workplace. Additionally, as noted in the CEQ report, dangers and potential dangers to the human reproductive system can come from a wide variety of sources unrelated to working conditions. For instance, poor maternal health, inadequate diet, the use of tobacco and alcohol, and the possible effects of chemical exposures in the environment and in the home, as well as in the workplace, all have the potential for affecting human reproduction. This multicausal nature of reproductive toxicity makes it exceedingly difficult to attribute a particular share of the problem to any one of these factors. The report notes that it is "fairly difficult" to identify reproductive hazards for occupational exposures to hazardous chemicals and "very difficult" for general environmental exposures. Thus, the state of awareness of the occupational setting as a factor in the etiology of human reproductive impairment is limited and does not permit sufficient generalizations about the nature and extent of reproductive effects on which to base regulation, other than on a case-by-case basis.

Lack of information, then, makes it impossible for OSHA to address workplace reproductive hazards as a generic issue. The agency has to deal with such hazards on a case-by-case basis. Thus, OSHA considers reproductive hazards as part of the total picture of hazards to human health. In the past, OSHA has responded to protect employees when appropriate and will continue to do so. For example, in its standard for occupational exposure to lead, in addition to other hygiene measures, OSHA requires that exposed employees must be trained and counseled on the dangers of lead to the reproductive system.

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In addition, in the area of training and education, OSHA has provided grants to projects in which non-profit organizations provide information for workers on the potential hazards of chemical exposures to the reproductive system.

In summary, OSHA, as a regulatory agency can act only on the basis of scientific knowledge, and for that knowledge, it must rely on the scientific community. Thus, OSHA is closely following the progress of research in this area and will continue to consider the scientific evidence on reproductive hazards as part of its general health standards activities.

Thank you, Mr. Chairman. I will be happy to answer any questions you and Members of the Subcommittee may have.

Mr. GORE. Thank you very much.

Our final witness is Dr. Gary Flamm, Acting Associate Director for Toxicological Substances of the Bureau of Foods over at FDA. Welcome, Dr. Flamm, please proceed.

Dr. FLAMM. Thank you very much, Mr. Chairman.

The Food and Drug Administration is pleased to participate in the hearing, and welcomes the opportunity to highlight its activities relating to the general area of reproductive effects and hazards.

The thalidomide tragedy of the mid-1960's dramatically demonstrated how vulnerable a developing human embryo can be to certain types of exogenous insults. Indeed, it became apparent from that incident that a teratogenic effect could occur in the absence of any overt maternal toxicity.

Following this thalidomide episode, the agency began immediately to reexamine its regulatory science policy to determine what additional research was needed to insure the safety of drugs and food additives when consumed by pregnant women.

The result of this reexamination was the establishment of new toxicological testing requirements for the premarket approval of drugs and food additives. These test requirements, which have been in effect for drugs since 1966 and for food additives since the early 1970's, include extensive investigation of factors which relate to reproduction toxicology, such as litter size, death of the conceptus, presence or absence of gross structural malformations, functional impairment, altered growth and developmental patterns.

For drugs, FDA recommends a sequential approach to testing in animals, including long-term and short-term treatment before pregnancy, during pregnancy and during the neonatal period.

The Bureau of Foods within the Food and Drug Administration, reflecting concern about long-term exposure to food additives, relies on the use of multigeneration reproductive studies in rodents and other laboratory animals with what is called a teratology phase to provide critical information on all the above issues of concern.

In addition, these tests can reflect disturbances in gonadal function, estrous cycles, mating behavior, conception, parturition, lactation, weaning and growth, and development of the offspring.

As indicated, for human drugs, FDA recommends specific animal reproduction tests that are divided into three distinct segments, each related to a particular area of mammalian reproduction.

The first segment is the general study of fertility and reproductive performance. The second, a teratology study; and the third, a perinatal and postnatal study.

Submission of segments I and II reproduction studies showing acceptable evidence of lack of teratogenicity and fetotoxicity at appreciable drug dosages must precede investigation of a new drug in women who are pregnant or who may become pregnant.

For drugs not intended for use in obstetrics or gynecology or for a rare or life-threatening disease, there should be adequate evidence of safety and efficacy from early clinical studies to support the inclusion of women of childbearing potential in the study.

FDA also conducts in-house reviews of human and animal data through periodic meetings of its task force on maternal and child problems. Evidence of potentially significant reproductive toxicity is often evaluated with the assistance of outside experts and consultants in determining appropriate regulatory action.

We are currently increasing our data base on birth defects that might be related to drug exposure by expanding the questions on reproduction included in the monitoring case reports, which have been received since 1969, and by comparing those reports to epidemiological studies from the Boston University Drug Epidemiology Unit, the Boston University Drug Surveillance program, and programs at the University of California and Yale University.

We are also using Michigan medicaid data involving approximately 28,000 deliveries. We expect that these data will increase by about 32,000 deliveries yearly. FDA also collaborates closely with the Centers for Disease Control in Atlanta, Ga., and the International Birth Defects Surveillance Center, and utilizes, to the extent possible, these data bases as well.

In the area of radiation, we know that irradiation during prenatal development can produce a variety of biological effects. Experimental studies with animals and human epidemiological studies and case reports, many of which have been conducted by FDA's Bureau of Radiological Health, have indicated that exposure to X-rays, or ionizing radiation, represents a hazard to the unborn child.

For example, research in rodents has established that grossly visible effects are possible from radiation doses in the range of 5 to 12 rads received during early pregnancy. Many of these defects involve faulty development of the central nervous system.

Later in pregnancy, radiation exposure can alter behavior, learning and coordination. Other experimental radiation effects include interference with the expression of genetic information and retarded growth and development.

The Bureau of Radiological Health has embarked on a program aimed at educating clinicians and their patients about the potential hazard of ionizing radiation of X-rays administered during pregnancy.

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For example, in August of last year, 1981, the Bureau issued recommendations to make physicians more aware of the need to consider pregnancy status and to assist them in deciding on whether to order, modify or forego certain X-ray examinations.

In July of 1980, a policy statement was issued by the Bureau of Radiological Health recommending against the use of X-ray in examining the maternal pelvis and fetal head, except in special critical circumstances. This policy has been endorsed by the American College of Radiology and a similar policy was adopted by them.

We have worked with the Department's Health Care Financing Administration to assess the impact of this information when used as part of an educational program in over 100 U.S. hospitals. Thus far, we have observed a three to five-fold reduction in the use of these kinds of X-ray examinations.

In addition, as part of an overall nationwide consumer education campaign on diagnostic X-rays, the Bureau of Radiological Health has distributed some 150,000 posters, developed in cooperation with the American College of Obstetrics and Gynecology for display in physicians' offices and hospital radiology waiting rooms, alerting women to advise their doctors about possible pregnancy.

In the area of diagnostic ultrasound, the Bureau is engaged in a number of experimental studies designed to evaluate possible biological effects such as carcinogenesis, teratogenesis, and effects on growth and development, as well as the biophysical mechanisms that may produce the cellular changes resulting from ultrasound exposure.

FDA has undertaken a number of actions to minimize exposure of the fetus. Included in these is FDA's work with ultrasound manufacturers to develop a voluntary performance standard for these devices, and the dialog that we have established with various professional organizations to explore the possibility of joint policy statement on ultrasound screening during pregnancy.

Although various bureaus have conducted tests and have required tests for reproductive effects over the past several years, the test results and their meaning are not always clear cut, nor is the degree to which animal tests predict for humans very well established. We need to know more about how to interpret animal test data.

It is particularly important that such research efforts in the comparison of humans and experimental animals be directed toward: One, fundamental processes of development and the mechanisms of malformation; two, the development of a sound data base on comparative pharmacokinetics and metabolism to provide more accurate and better ways of extrapolating animal data to man; three, the development of improved and validated procedures for detecting the full range of possible injury which might occur during the lifespan of the organism; and, finally, the development of in vitro tests for detecting teratological events.

A number of studies in these four areas are currently underway in laboratories within the Agency all involving multidisciplinary approaches to solving problems in developmental toxicology. For example—and this is just as an example—we are exploring studies on uterine and estrogen receptor development, on metabolic conversion and placental transport of the natural and synthetic estro-

gens, on the ontogeny of cardiovascular development and function, and the application of pharmacokinetics to the problem of predicting teratogenic effects from animal species to humans.

In addition to laboratory research, FDA has been involved in the development of approaches for assessing reproductive risks. FDA, in connection with the Interagency Regulatory Liaison Group, sponsored a workshop to establish criteria for assessing reproductive toxicity. This activity involved 80 to 90 participants from universities, industry, and government. Six major topics were discussed and included: One, reproductive endpoints; two, teratology endpoints; three, pharmacokinetics; four, reproductive mechanisms; five, teratology mechanisms; and six, risk assessment statistics. The results of the workshop will be published as a scientific report and made available to participants of the workshop and others in the scientific community.

A workshop sponsored by FDA/IRLG/EPA met last August to evaluate the applicability of in vitro test systems as a screen for potential teratogens. This was to encourage those interested in developing these systems to establish a well-controlled approach to validation, and assist those interested in the application of such systems to use them in the overall risk assessment process. The proceedings of this workshop will be submitted for publication in the Journal of Teratogenesis, Carcinogenesis and Mutagenesis.

The National Toxicological program is developing improved testing and methods for evaluating birth defects, fertility and male and female reproductive capacity. Both our Bureau of Foods and the National Center for Toxicological Research—which is a bureau-level activity within FDA—are participants in these efforts. A major focus is the validation of in vivo and in vitro test methods which can be used for screening all types of potentially toxic agents.

In conclusion, the agency continues to review and has established toxicological test requirements identifying potential agents that represent a hazard to reproduction. It is actively engaged in research to improve the understanding of effects on reproduction, how to measure them and how to interpret test data in terms of public health impact. This has and continues to involve coordinated efforts among scientists in academia, industry, and government.

Again, thank you, Mr. Chairman, for this opportunity to discuss this important issue.

[The prepared statement of Dr. Flamm follows:]

STATEMENT BY DR. GARY FLAMM

Mr. Chairman, the Food and Drug Administration (FDA) is pleased to participate in this hearing and welcomes the opportunity to describe its activities relating to the general area of reproductive effects and hazards.

BACKGROUND

Before the thalidomide tragedy of the 1960's, it was generally assumed that the in utero child was physically isolated and protected from most forms of environmental hazards. The thalidomide tragedy however, dramatically demonstrated how vulnerable a developing human embryo can be to certain types of outside insults. It became apparent that a teratogenic effect could occur in the absence of overt maternal toxicity.

Following the thalidomide episode the Agency began immediately to reexamine its regulatory science policy to determine what additional research was needed to

ensure the safety of drugs and food additives when consumed by pregnant women. The result of this reexamination was the establishment of new toxicological testing requirements for the premarket approval of drugs and food additives. These test requirements, which have been in effect for drugs since 1966 and for food additives since the early 1970's, include an extensive investigation of relations to reproduction such as liter size, death of the conceptus, presence or absence of gross structural malformations, functional impairment, altered growth, and development patterns.

FDA's National Center for Drugs and Biologics recommends a sequential approach to testing in animals, including long-term and short-term treatment before pregnancy, during pregnancy and during the neonatal period. The Bureau of Foods, reflecting concern about long-term exposure to food additives, relies on the use of multigeneration reproduction studies in rodents and other laboratory animals with what is called a teratology phase to provide critical information on all the above issues concerned. In addition, these tests can reflect disturbances in gonadal function, estrous cycles, mating behavior, conception, parturition, lactation, weaning and growth, and development of the offspring.

DRUGS

The sequence of preclinical or animal testing before the new drugs are introduced to humans generally involves single dose acute toxicity studies in several animal species and additional toxicological tests of up to three months in a rodent and nonrodent species. In the latter studies, assessments are made of behavioral and physical defects, including gross and microscopic examination of endocrine and reproductive organs.

FDA recommends specific animal reproduction tests that are divided into three segments, each related to an area of the mammalian reproductive process: (I) general study of fertility and reproductive performance, (II) teratological study, and (III) perinatal and postnatal study. Submission of segments I and II reproduction studies showing acceptable evidence of lack of teratogenicity or fetotoxicity at appreciable drug dosage must precede investigation of a new drug in women who are pregnant or who can possibly become pregnant. For drugs not intended for use in obstetrics or gynecology or for a rare or life-threatening disease, there should be adequate evidence of safety and efficacy from early clinical studies to support the inclusion of women of childbearing potential in the study.

FDA conducts in-house reviews of human and animal data through periodic meetings of its Maternal and Child Problem Task Force. Evidence of potentially significant reproductive toxicity is often evaluated with the help of outside consultants to determine appropriate regulatory action.

We are expanding data on birth defect drug exposure questions by monitoring case reports which have been received since 1969 and by comparing these reports to epidemiological studies from the Boston University Drug Epidemiology Unit, the Boston University Drug Surveillance Program, the University of California, and Yale University. We are also using Michigan Medicaid data involving approximately 28,000 deliveries. These data will expand by about 32,000 deliveries yearly. FDA collaborates closely with other important data sources, including the studies of the Centers for Disease Control, international birth defects surveillance, and other studies.

RADIATION

Irradiation during prenatal development can produce a variety of biological effects. Experimental studies with animals and human epidemiological studies and case reports, many of which have been conducted by the FDA's Bureau of Radiological Health (BRH), have indicated that exposure to X rays (or "ionizing" radiation) represents a hazard to the unborn child. For example, research in rodents has established that gross visible effects are possible from radiation doses in the range of 5 to 12 rads received during early pregnancy. Many of these defects involve faulty development of the central nervous system. Later in pregnancy, radiation exposure can alter behavior, learning, and coordination. Other experimental radiation effects include interference with expression of genetic information and retarded growth and development.

Another effect of radiation exposure in utero is carcinogenesis. In collaboration with the Colorado State University, the BRH has supported a major study begun in 1962 to conduct a lifetime evaluation of beagle dogs exposed to prenatal and early postnatal ionizing radiation. Although the study is not yet completed, we have observed excess cancers in the irradiated groups. We expect that the final results will

provide a rationale for the epidemiologic observations of radiation-induced cancers, and provide more quantitative risk estimates.

Based on this study and other research, BRH has embarked on a program aimed at educating clinicians and their patients about the potential hazards of X rays administered during pregnancy. For example, in August of last year, the Bureau issued recommendations to make physicians more aware of the need to consider pregnancy status and to assist them in deciding on whether to order, modify, or forgo certain X ray examinations. In July 1980, a policy statement was issued by BRH recommending against the use of X ray pelvimetry (an X ray examination used to provide measurements of the maternal pelvis and fetal head) except in special circumstances. This policy has been endorsed by the American College of Radiology and a similar policy was adopted by the American College of Obstetricians and Gynecologists.

We have worked with the Department's Health Care Financing Administration (HCFA) to assess the impact of this information when used as part of an educational program in over 100 U.S. hospitals. Thus far, we have observed a three- to five-fold reduction in pelvimetry use rates. In addition, as part of an overall nationwide consumer education campaign on diagnostic X rays, the BRH has distributed some 150,000 posters, developed in cooperation with the American College of Obstetricians and Gynecologists for display in physicians' offices and hospital radiology waiting rooms, alerting women to advise their doctors about possible pregnancy.

In the area of diagnostic ultrasound, the Bureau is engaged in a number of experimental studies designed to evaluate possible biological effects such as carcinogenesis, teratogenesis, and effects on growth and development, as well as the biophysical mechanisms that may produce the cellular changes resulting from ultrasound exposure. FDA has undertaken a number of actions to minimize exposure of the fetus. Included in these is FDA's work with ultrasound manufacturers to develop a voluntary performance standard for these devices, and the dialogue we have established with various professional organizations to explore the possibility of joint policy statement on ultrasound screening during pregnancy.

STATUS OF RESEARCH

Although our various Bureaus have conducted or reviewed test results on reproductive effects for several years, these test results and their meaning are not always clear cut, nor is the degree to which the animal tests predict for humans very well established. We need to know more about how to interpret animal test data. It is particularly important that such research efforts in the comparison of humans and experimental animals be directed toward: (1) fundamental processes of development and the mechanisms of malformation (teratogenicity); (2) the development of a sound data base on comparative pharmacokinetics and metabolism to provide more accurate ways of extrapolating animal data to man; (3) the development of improved and validated procedures for detecting the full range of possible injury which might occur during the lifespan of the organism; and (4) the development of in vitro tests for detecting teratological events.

A number of studies in these four areas are underway in laboratories within the Agency and involve multidisciplinary approaches to problems in development toxicology. For example, we are exploring studies on uterine and estrogen receptor development, on metabolic conversion and placental transport of the natural and synthetic estrogens, on the ontogeny of cardiovascular development and function, and the application of pharmacokinetics to the problem of predicting teratogenic effect from animal species to man.

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workshop will be submitted for publication in the Journal of Teratogensis, Carcinogenesis and Mutagenesis.

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SUMMARY

In conclusion, the Agency continues to review and has established toxicological test requirements identifying potential agents that represent a hazard to reproduction. It is actively engaged in research to improve the understanding of effects on reproduction, how to measure them and how to interpret test data in terms of public health impact. This has and continues to involve coordinated efforts among scientists in academia, industry, and Government.

Again, thank you, Mr. Chairman, for this opportunity to discuss this important issue.

Mr. GORE. Thank you very much.

Dr. Hueter, are you familiar with the R&D plan just prepared and submitted to Congress by EPA?

Dr. HUETER. Yes; I am familiar with the developmental biology piece of that plan. Is that your question, sir?

Mr. GORE. Yes; it sort of establishes research priorities and maps out a plan, a 5-year research plan. It is quite late in being submitted to the Congress. It was like pulling eyeteeth to get it out of EPA but, in any event, it was submitted 2 weeks ago.

I am wondering where the research into reproductive hazards appears in that 5-year plan?

Dr. HUETER. The reproductive developmental biology research program should show in that plan in the decision units associating themselves with pesticides, with the toxics program, with the hazardous air pollutant program, and also with the waste program.

Mr. GORE. What is the level of effort on the reproductive hazards in that plan? If you are not familiar with it, we will let you submit a response for the record, if you want to do it that way?

Dr. HUETER. Are you referring to the fiscal year 1983 program?

Mr. GORE. I am talking about the 5-year plan.

Dr. HUETER. I will have to submit that for the record, sir.

Mr. GORE. OK.

[The information follows:]

While the Research Outlook 1982 (EPA-600/9-82-006) does not discuss reproductive research or risk assessment at length, it does mention such activities under the program description for hazardous air pollutants, mobile sources, non-ionizing radiation, pesticides, toxic chemical testing and assessment, and water quality. While no mention was made of reproductive studies under the drinking water section, EPA does conduct studies on the reproductive effects of drinking water contaminants.

The resources reported in the Research Outlook 1982 are aggregated across the Office of Research and Development. The FY-82 current estimate is given and projected figures for 1983-86 are provided for no growth, moderate growth, and high growth scenarios. The resources are broken out by program (hazardous air pollutants, pesticides, etc.) only. There is no break-out for reproduction. EPA has established research risk assessment programs in the reproductive area and a pattern of growth for these programs. Research and risk assessment resources for reproduction have roughly doubled in the last six years. While it would be premature to discuss the FY-84 budget, EPA does plan to continue work on reproductive effects and none of the scenarios in the Research Outlook suggest reductions in this area.

Mr. GORE. We have had some indications that the amount of attention assigned to this problem in the 5-year plan is not really

commensurate with the expressions of concern that we have had. But we will have your response for the record.

Let me move to some specific case studies, some that we got into preliminarily earlier. I would like to ask you about this Oryzalin case. The pesticide is also called Surflan. Are you familiar with this pesticide?

Dr. HUETER. Not personally, but Dr. Johnson, who is accompanying me, certainly is.

Mr. GORE. Perhaps he could join us at the witness table. Could you identify yourself to the reporter please.

Dr. JOHNSON. Thank you, Mr. Chairman.

I am Ed Johnson, Director of the Office of Pesticide Programs in the Environmental Protection Agency.

Mr. GORE. Thank you.

Several years ago, concern was expressed by workers that Eli Lilly's plant in Rensselaer, N.Y., where Oryzalin is manufactured, that their exposure to the pesticide had caused birth defects in their children. Are you familiar with these concerns, Dr. Johnson?

Dr. JOHNSON. Yes, I am, Mr. Chairman. The concerns were reported to the Agency by the workers, in a joint meeting, I might add, with NIOSH and OSHA. The investigation of those concerns was conducted by members of the staff.

Mr. GORE. By EPA?

Dr. JOHNSON. That is correct.

Mr. GORE. In support of its production of Oryzalin, Eli Lilly submitted a study concerning the effect Oryzalin had on rabbits, a study that essentially concluded that there were no reproductive hazards associated with Oryzalin. Are you familiar with that study?

Dr. JOHNSON. I am not familiar with the details of the study, although I am familiar with the fact that there was a rabbit teratology study which was submitted along with the total data base for the registration of that chemical.

Mr. GORE. And that study was submitted to the EPA?

Dr. JOHNSON. Yes; that is correct.

Mr. GORE. Could you provide the subcommittee with a copy of that study?

Dr. JOHNSON. Yes, I can. I would prefer if the chairman would request it in writing as chairman of the committee, since we are having some issues with confidentiality of the data at the moment. We will be glad to provide that under conditions of confidentiality.

Mr. GORE. The initial study in question by Eli Lilly was heavily criticized by EPA, OSHA and NIOSH as inadequate and improperly done. Do you know what the basis of the Agency's criticism was?

Dr. JOHNSON. I don't know the details. There were a number of criticisms of the study. We requested as a result that the company redo the teratology study on the rabbits. There were a number of other studies on the data base as well, including a rat teratology study which the Agency did accept, and we believe it was negative, as well as three generational studies on reproductive effects which appeared to be adequately done.

The study was uncertain—I think that was the conclusion of the Agency—with respect to the rabbit. We have since received the redone rabbit study. My reviewers are looking at it right now. But

the conclusion of the study as stated is that the material was tested up to 125 milligrams per kilogram, and it does not show either fetotoxic or maternal toxicity or defects at that level.

Mr. GORE. So it is fair to say that the Eli Lilly research did not support its favorable conclusions about Oryzalin?

Dr. JOHNSON. I think one has to look at the toxicological data base in its entirety. When an EPA toxicologist makes a determination on a chemical, he does not make it generally based solely on a single study; he looks at the overall toxicological profile as evidenced by a wide range of studies. In this particular case, when the registration was issued, the reviewers felt that on the total profile of this compound, and given the ways in which it would be used, that it could be used safely as required under FIFRA for legal sale and use in the United States.

When the Agency became involved with the concerns of the workers, which we investigated, we wanted to see if we could take care of any uncertainties which might exist about the safety of Oryzalin. We did several things, one of which was to require a new study to resolve any uncertainties about that. We also investigated nine plants where Oryzalin was produced, and we have since investigated medical records of workers in production plants. We also looked at medical histories of people who mixed and applied Oryzalin in its use as an herbicide.

It really was the entire data profile that caused us to reach our conclusion in 1980, and the request for additional studies was to tie up some loose ends rather than to plug a major deficiency.

Mr. GORE. My last question was actually kind of a limited question. The research provided to EPA by Eli Lilly at that point did not support its favorable conclusions about Oryzalin; is that a fair or unfair statement?

Dr. JOHNSON. Yes, I guess if one looked at that study alone and applied current-day standards to that study, one would say that the study might not have been up to current-day standards.

Mr. GORE. OK.

Dr. Robert Beale, who was then with OSHA, was especially critical of the Eli Lilly study. He believed that Eli Lilly's research actually provided some reason to conclude Oryzalin might have an adverse effect on fetuses. Is that your recollection of it?

Dr. JOHNSON. I recall that that was the opinion of Dr. Beale.

Mr. GORE. And he filed a report with EPA outlining those concerns; is that correct?

Dr. JOHNSON. I believe so.

Mr. GORE. Could you provide us with a copy of that report?

Dr. JOHNSON. Yes, I can.

Mr. GORE. Because of the concerns expressed over its initial Oryzalin study, Eli Lilly was directed by EPA in early 1980 to conduct additional tests on Oryzalin's effect on laboratory animals. You indicated that in an earlier response.

Exactly what did you ask Eli Lilly to do or direct them to do?

Dr. JOHNSON. We asked for two things, as I recall. One was to redo the rabbit teratology study, and the second was to provide medical information on workers at production plants that were under the control of Eli Lilly.

Mr. GORE. I am sorry, but we have a tie vote in the Intelligence Committee. I apologize to you. We will have to adjourn for 15 minutes.

[Recess.]

Mr. GORE. The subcommittee will come to order. I apologize to our witnesses and guests.

Mr. Johnson, we were having this discussion about what you told Eli Lilly to do after the initial concerns were expressed.

Dr. JOHNSON. Yes. We asked Eli Lilly, as I recall, to re-do the rabbit teratology study, and also to provide us with some medical information on workers in manufacturing plants that were under their control.

Mr. GORE. Have they done that?

Dr. JOHNSON. Yes, both of those have been provided.

Mr. GORE. Could you provide the subcommittee with a copy of those?

Dr. JOHNSON. Yes, I will. I will add it on to your written request.

Mr. GORE. Thank you.

Has EPA reviewed the new Eli Lilly studies?

Dr. JOHNSON. We have reviewed the worker data that came in several months ago, and we found nothing to cause us concern in those data. We have had the rabbit teratology study for only a few weeks, I believe, and it has not yet been fully reviewed. We have had a cursory look. The highest levels tested, as I said earlier, does not seem to show any effects, either maternal toxicity or on the offspring. But we will reviewing that in more depth over the next 10 days, I believe.

Mr. GORE. Again, Eli Lilly's conclusion is the same, that it is safe and there is no reproductive hazard?

Dr. JOHNSON. Yes, that is correct.

Mr. GORE. And EPA tentatively agrees with that conclusion; is that correct?

Dr. JOHNSON. Yes, that is correct.

Mr. GORE. You say that you are going to be reviewing the studies submitted. Is EPA planning to have some kind of written report or conclusion about Oryzalin?

Dr. JOHNSON. EPA formed a written conclusion in March 1980, which was publicly released. If the reviewers' conclusions do not differ when the current review is completed, we will merely document that for the record because it would not indicate any further regulatory action and would merely corroborate the conclusion that we reached in 1980, so there wouldn't be any public announcements to that effect.

Mr. GORE. If you do have a subsequent written report or conclusion, we would appreciate it being provided for the record.

Dr. JOHNSON. There will be a reviewers' report on the study itself.

Mr. GORE. You can provide that to us.

Dr. JOHNSON. Yes.

Mr. GORE. Does the EPA have any independent basis, other than the data submitted by Eli Lilly, for concluding that the rate of congenital abnormalities among the children of the employees in Rensselaer is not unusual?

Dr. JOHNSON. I don't believe that that was exactly our conclusion. We felt that the rate of congenital abnormalities in the workers' offspring was in fact unusual. Those types of effects are seen very rarely in the small population that was exposed. One would not expect to see them with the frequency that occurred.

The issue that we are addressing is, of those effects which we did consider to be unusual, was it likely that they were caused by Oryzalin or is it likely that they might have been caused by something else in the workplace. Oryzalin was produced under contract by GAF. It was a GAF-owned plant that produced the material for ELANCO under contract. That batch process also produced a number of other chemicals. There is some indication, based on epidemiological work, that it was a fairly sloppy operation in terms of the way the batch processing was operated, not only for Oryzalin, but for a number of chemicals.

Also, Dr. Hook—I believe his name was—an epidemiologist in the State of New York, did extensive work and reached the conclusion that it was unlikely as well that Oryzalin caused this effect.

In addition, we went to nine plants where Oryzalin is currently produced, and we did some epidemiological work with applicators of the pesticide. We did not find anything in those examinations that would lead us to believe that there was any problem associated with the use or production of Oryzalin.

Mr. GORE. Let me pin down the question of the rate of congenital abnormalities. The staff of the subcommittee was told by a member of your staff actually reviewing Eli Lilly studies that he did not consider the incidents of congenital abnormalities to be unusual. Perhaps there is a communications problem. But it is your testimony here today that, in your opinion, that rate is unusual.

Dr. JOHNSON. Maybe it is a communications problem. It sounds like it probably is. We feel that the rate observed in the workers at the plant in Rensselaer appears to be unusual.

Mr. GORE. Yes.

Dr. JOHNSON. But that is not what one would expect to see.

In reviewing the animal studies of Oryzalin submitted to us by ELANCO, we do not see any unusual levels of birth defects in those studies. That may be what the communication problem was.

Mr. GORE. OK. As a result of the animal study?

Dr. JOHNSON. Yes, that is correct.

Mr. GORE. Do you know of any chemicals that are known to produce congenital abnormalities in humans that do not show up in animal tests?

Dr. JOHNSON. I am getting out of my field. I have not personally been told of any.

Mr. GORE. Has anybody else here? Thalidomide is the most prominent example.

Were there frequent meetings between EPA officials and Eli Lilly representatives while Eli Lilly was preparing its new studies?

Dr. JOHNSON. Do you mean between the time of our initial conclusion and the submission of the new studies?

Mr. GORE. Yes.

Dr. JOHNSON. I don't know whether they were numerous. We, as a matter of course, have discussions about protocols to see if they are appropriate and to make sure that the test results are what we,

in fact, want. I was not personally involved in any of those. My staff may well have met with them on that basis.

Mr. GORE. Are you aware that NIOSH has been conducting its own review of the problems at the Rensselaer plant?

Dr. JOHNSON. Yes, I am. We work very closely with them. I personally met and my staff met many times with both OSHA and NIOSH to discuss the situation. We are interested both in their findings on the plant at Rensselaer, as well as any other findings they may have in looking at any other plants that produce Oryzalin.

Mr. GORE. So you do have a mechanism for coordinating that effort?

Dr. JOHNSON. Yes, we do. We have an agreement with NIOSH that has been in effect for some years to share information and results of studies. We try to work quite closely together on these.

Mr. GORE. Have you shared with NIOSH the new Eli Lilly studies?

Dr. JOHNSON. I do not believe so.

Mr. GORE. Why not?

Dr. JOHNSON. I think probably because they are new enough that we haven't shared them yet. We have just received them. As I said, the worker study was received some time ago, but the rabbit study was just recently submitted.

Mr. GORE. Did you just get them last week?

Dr. JOHNSON. The rabbit study has been in a few weeks, and the worker data has been in, I guess, for several months.

Mr. GORE. Several months?

Dr. JOHNSON. Yes.

I won't guarantee we haven't shared it. I would have to go back and check that. But I would expect we may not have.

Mr. GORE. That would seem to be not the best coordination or exchange of information if you have had it for several months and they haven't had it. That was just a comment.

Is EPA aware that NIOSH considers the birth defect rate distinctly unusual and far above the national average at Rensselaer?

Dr. JOHNSON. Could you repeat that?

Mr. GORE. Are you aware that NIOSH finds the rate of birth defects at Rensselaer "distinctly unusual" and far above the national average?

Dr. JOHNSON. Yes, I am. It would be consistent with my remark earlier that I think we probably reached that conclusion during our joint investigation in the early days of the study.

Mr. GORE. The mechanism for resolving the findings of your agency with those of NIOSH is what, just an informal series of conversations?

Dr. JOHNSON. Yes, we will continueto work back and forth informally. Right now, I don't believe that there are any issues. We studied Oryzalin, per se, and they studied the plant at Rensselaer. If we do find that their studies indicate something different with respect to the properties of Oryzalin, then we will reopen our investigation to see whether any additional regulation is necessary.

Conversely, if we find something that looks different than what we collectively thought some time ago, we will then make that available to NIOSH, and see what that means for our conclusion.

Mr. GORE. You agree with NIOSH that there is a distinctly unusual, quite high rate of birth defects among the employees at the Rensselaer plant.

Dr. JOHNSON. Yes, that is correct.

Mr. GORE. Are there other chemicals also made at the Rensselaer plant?

Dr. JOHNSON. At the time Oryzalin was produced, yes, there were a substantial number of other chemicals produced in the same building where these workers were employed, in addition to Oryzalin.

Mr. GORE. What were the other chemicals?

Dr. JOHNSON. I don't have them here. I can provide those for you.

Mr. GORE. What do these employees have a right to expect from the agencies that are represented here? I know it is a confusing and difficult subject, but if a group of employees find at their coffee break or just in informal conversations that there is this very high rate of birth defects among their children, and they come to the Government agency, the agency asks the company to submit a rabbit study and it shows that the chemical suspect doesn't produce problems in rabbits, is that the end of it? What happens after that?

Dr. JOHNSON. I think you have to divide it up into a couple of areas. The reason we are working together with NIOSH and OSHA is because there is a division of legal responsibility between protection in the workplace, and protection for people from pesticides once they leave the work environment and actually become pesticides in the market and residues on food, and so forth.

Mr. GORE. Yes.

Dr. JOHNSON. We felt that there were different jurisdictional responsibilities, but that we all could share information and share scientific talent. That is the reason why we felt we ought to get together to work on this.

We, for our part, believe that when one of these concerns is brought to our attention, particularly concerns that are brought from the workplace where there may be high exposure, that we have a responsibility to investigate those because they may demonstrate that there are effects at lower levels which have gone unobserved in users of pesticides. That, in fact, is what we did.

I won't speak to what OSHA or NIOSH believes they ought to do in the way of followup, but we did follow up quite extensively, including, as I said, going back into the manufacturing establishment to try to get some epidemiological evidence to determine whether there was a problem, and also looking at pesticide applicators who might be among the more highly exposed users of pesticides. So we believe we have a responsibility to follow up on those allegations.

Mr. GORE. Fine. Thank you.

Let me ask you, Dr. Vance, about the anesthetic gases. An affidavit of August 17, 1981, almost a year ago, signed by Mr. Auchter, states that "Anesthetic gases, including nitrous oxide, cause statistically significant increases in miscarriages and congenital abnormalities."

Given the fact that large segments of the population are exposed to these gases, in hospitals, dental offices, and workplace environments, what conclusion has OSHA come to regarding the issuance

of a standard for nitrous oxide at the level recommended by NIOSH, 25 parts per 1 million?

Dr. VANCE. OSHA is not presently doing work on anesthetic gases, Mr. Chairman. I am not familiar with the affidavit you are speaking of. I have been at OSHA for approximately 3 months. As a matter of fact, today is exactly the end of those 3 months.

But I will be happy to inquire into that and find out what the history of the regulatory on nitrous oxide is and what became of it, and supply it for the record. But I am prepared to say right now that no one on the staff of the Health Standards directorate in OSHA is actively engaged in doing work on nitrous oxide right now.

Mr. GORE. I don't quite understand. I will ask unanimous consent to put into the record this affidavit here. It is in a court case, a matter of public record. It is an affidavit of Thorn Auchter. He says that there is evidence tending to show that occupational exposure to nitrous oxide results in a statistically significant increase in spontaneous abortion, as well as an increase in congenital abnormalities in children born to spouses of males and females who are exposed to nitrous oxide.

Our panel of expert witnesses earlier expressed the same conclusion with respect to anesthetic gases, including nitrous oxide. NIOSH has recommended the issuance of a standard. Yet, there isn't one, and you say that no one is working on one.

Dr. VANCE. I understood you to say, Mr. Chairman, that there is a standard.

Mr. GORE. There is an OSHA standard?

Dr. VANCE. I understood you to say that.

Mr. GORE. No. There is a NIOSH recommendation, and there has been for quite some time.

Dr. VANCE. There is not presently a group of people working on anesthetic gases in OSHA.

Mr. GORE. Why not?

Dr. VANCE. As I say, I have been there for 3 months. When I came in, I was presented, Mr. Chairman, with a series of projects which OSHA had in progress and with directions to bring subsequent projects to the attention of the Assistant Secretary and to his Deputy as they arose, as my attention was drawn to them from any of a myriad of sources, such as, for example, possibly a meeting like this today. Among those projects which I was given direction to shepherd through the regulatory process, there were some 15 to 18 different ongoing activities, some of which have been discussed here today, ethylene oxide, lead, ethylene dibromide. Among those, anesthetic gases was not included.

Mr. GORE. Why not?

Dr. VANCE. I don't know.

Mr. GORE. Let me tell you that the NIOSH standard, the one they recommend, is 25 parts per million. According to Thorn Auchter in this sworn affidavit, "prevailing exposure levels range from several hundred to several thousand parts per million, with the highest exposures to dental workers."

You have medical evidence that people in the workplace who want to have children have their children threatened as a result of exposure in the workplace. The medical experts have agreed on it;

OSHA agrees with it; NIOSH recommends the standard; and the standard recommended is grossly below what the prevailing exposure level is for an estimated 254,000 American workers.

Dr. VANCE. Mr. Chairman, the prioritization that was in place at OSHA when I came on board at OSHA had obviously been set over a substantial period of time prior to that.

Mr. GORE. That is very interesting. Let me describe the context of this affidavit. This is OSHA's explanation of why it can't do something else. The reason it can't do something else, in part, is that it is working on anesthetic gases. The end of the statement on anesthetic gases by Mr. Auchter says, "The project currently requires the work of one person full time and one person part time."

Lest I get you into a conflict with Mr. Auchter, let me hasten to add that this is dated in August 1981. So, presumably, the person that was alleged to have been working full time on that back then isn't anymore.

Dr. VANCE. Mr. Chairman, I receive regular reports of all of the activities of the 35 or so professionals that are health scientist progressionals that are on the Health Standards directorate. I can tell you that there is no one working on anesthetic gases.

Mr. GORE. But you can't tell us why no one is.

Dr. VANCE. That is correct.

Mr. GORE. OK. It sounds like someone should be, doesn't it?

Dr. VANCE. I will certainly look into it. I don't know the history of this incident or what is behind it.

Mr. GORE. It is not just an incident, it is 254,000 American workers that are exposed to it on a continuing basis today.

Dr. VANCE. A substantial number of workers. As you know, Congress gave us a scheme for prioritizing our standards development process and the number of workers who are exposed are one of the elements that we look at as part of our risk assessments.

Mr. GORE. OK.

Could you get back to us on that.

Dr. VANCE. I certainly will.

Mr. GORE. It certainly seems like something that ought to be done.

Dr. VANCE. I certainly will, Mr. Chairman.

[The information follows:]

Insert, p. 152:

The affidavit to which Chairman Gore referred was prepared in response to a Court of Appeal's decision in National Congress of Hispanic American Citizens (El Congresso), et al, v. Ray Marshall, Secretary of Labor, et al. 626 F. 2nd 882 (D.C. Cir. 1979) and its order of June 9, 1981. The Court of Appeals, in remanding this case, required the Secretary to file a timetable for development of an OSHA field sanitation standard. Assistant Secretary Auchter's affidavit on behalf of the Secretary of Labor was made to comply with the Court of Appeal's order that the timetable must be a "good faith representation" of the Secretary's reasonable expectation as to when the field sanitation standard would be forthcoming.

In the affidavit, Mr. Auchter listed all the standards development projects, both high and lower priority, that OSHA had under way at the time (August 1981).

OSHA's basic tool for setting regulatory priorities is provided by Section 6(g) of the Act which states in part that:

> In determining the priority for establishing standards under this Section, the Secretary shall give due regard to the urgency of the need for mandatory safety and health standards for particular industries, trades, crafts, occupations, businesses, workplaces or work environments...

In addition, statutes such as the Regulatory Flexibility Act of 1980 and Executive Order 12291 require periodic, systematic review of existing regulations.

Mr. Auchter states in the affidavit that for "an initial two-year period... all appropriate personnel are dedicated to the development of higher priority standards than the field sanitation standard." (It should be noted that anesthetic gases, including nitrous oxide, were listed in the group of lower priority standards in the affidavit.) Mr. Auchter stated that work on a field sanitation standard could not even be initiated until this two-year period had passed, without necessitating a cessation of work on one or more of the projects already underway.

The Court, however, disagreed with OSHA's five-year schedule for development of a field sanitation rule and ordered completion of a standard within eighteen months, thus requiring a change in the allocation of Agency staff resources.

Thus, since the affidavit of August 17, 1981, was submitted to the court, OSHA has had to revise its priorities in consideration of the availibility of staff and monetary resources as well as of the objective data necessary for OSHA to promulgate enforceable regulations. OSHA currently has nineteen health standards under active development. Agency resources for health standards-developments are stretched to the limit. Of the twenty-seven staff persons originally counted in the August, 1981, affidavit, only twenty-three are on OSHA's staff at present. Although there are a number of toxic substance exposures, including exposure to anesthetic gases, for which we feel regulatory action may be appropriate, OSHA does not have the resources to dedicate to such projects at this time. (See attached listing of projected health standards activity.)

Health Standards Activity 1981 - 1984

Directorate of Health Standards Programs

Standard	Final Rule
Access to Employee Exposure and Medical Records-revision	1983
Arsenic-Final decision on significance of risk issues	1983
Carcinogen Policy - Revision	1983
Coal Tar Pitch Volatiles - Revision	1982
Ethylene Dibromide	1983
Ethylene Oxide	1984
Hazard Communication	1983
Hearing Conservation - Revision	1982
Laboratories, Exposure to Toxic Substances in	1984
Lead - Revision	1983
Noise	1984
QNFT vs. QLFT	1982
Radiofrequency Radiation	1984
Respiratory Protection	1984

Mr. GORE. What about recordkeeping requirements. With an estimated 254,000 workers exposed to nitrous oxide alone, not to mention the other anesthetic gases, what recordkeeping requirements do you feel OSHA should issue so that early reproductive problems are effectively monitored and quickly discovered?

Dr. VANCE. OSHA does have recordkeeping requirements that are part of its access to medical records standard. As I am sure you are aware, Mr. Chairman, the access-to-medical-records standard is in a state of review right now with a view toward determining how long medical records of employees should be maintained.

OSHA is also in the process, Mr. Chairman, of taking public comment. In fact, public comment is being received today in Detroit on a proposed hazardous-communications standard which would require industries to maintain records and to inform employees of the nature and existence of health hazards. Among those health hazards are reproductive hazards. We refer to those in the testimony that I gave to you. I will be glad to expand on that a little bit, if you want, Mr. Chairman.

Mr. GORE. Would that include the employees of these businesses, the hospitals and industrial establishes, with nitrous oxide?

Dr. VANCE. The proposal covers SIC codes 20 through 39 and the chemical manufacturing industry generally. I am not sure what standard industrial code classifications hospitals fall into. If they fall within that classification, then it would cover them. Of course, this is a proposal, and one of the things which OSHA solicits is comment upon how broad the scope of this kind of hazard communications standard should be.

Mr. GORE. With regard to this information access, the proposed change, as I understand it, would drastically curtail the requirements that are presently in effect on employers. For example, the proposal cuts the number of hazards chemicals for which exposure records must be kept from approximately 40,000 down to 3,500, including the reproductive hazard mandate; is that correct?

Dr. VANCE. I think that that has to be—I am not sure about the numbers. There is a modification. I think that the access to medical records standard has to be viewed in concert with the proposed hazard communications standard as well. I think it has to be remembered that both of these are proposals on which public comment is solicited at that time. There is a complete package of proposed changes in the access-to-medical-records standard. I feel confident with the numbers that you are talking about, that your staff has probably advised you correctly, but I can't verify them.

[Additional information subsequently supplied follows:]

Material for the Record of the Hearings of July 27, 1982

Insert, p. 54:

The present OSHA regulation for Access to Employee Exposure and Medical Records (29 CFR.1910 part 20), went into effect on August 21, 1980, except for the construction industry (for which the standard became effective on September 15, 1981), and for the flavor and fragrance industry (for which the standard will become effective in February, 1983). In a Federal Register notice of July 13, 1982, OSHA sought public comment on proposed modifications to the records-access rule. The standard is being reviewed, in part, because of questions that have been raised about its broad definition of "toxic substance" and, in part, because of other questions that have been raised about coverage of employees who may be only briefly exposed to toxic substances and about adequate safeguards for trade secret information. The Regulatory Flexibility Act of 1980 also requires such review.

The existing standard defines "toxic substance" to include any substance listed in the National Institute for Occupational Safety and Health (NIOSH) Registry of Toxic Effects of Chemical Substances (RTECS) — a compendium of over 45,000 chemicals including such common substances as sugar and salt. OSHA has received numerous complaints from affected parties criticizing RTECS as being overinclusive. The current regulation also defines as "toxic" any substance regulated by any Federal law or rule for reasons of "hazard to health." This provision has been interpreted by some to mean that all food ingredients could be considered toxic since they are substances regulated by the Food and Drug Administration.

In the Federal Register notice of July 13, 1982, OSHA's proposed modification of the definition of "toxic substance" retains the use of RTECS as a basic source of information, but limits the list's application by adding specific toxicity criteria which would indicate whether or not a substance is likely to pose an occupational health risk. The proposed definition includes: (1) substances known by employers to be toxic; (2) substances known to be toxic to humans on the basis of information contained in Material Safety Data Sheets (MSDS); and (3) substances contained in RTECS which meet certain toxicological criteria. These criteria include: substances toxic to humans at any dose level, carcinogens and reproductive toxins based on animal testing at any dose level, and substances acutely toxic in animals through dermal, respiratory and ingestive routes of exposures. NIOSH has generated from RTECS a list containing 3,492 substances which meet these criteria. The proposed revised definition of "toxic substance," in OSHA's judgment, adequately delineates the scope of the regulation to include those substances which pose a risk of toxicity to workers.

There is also simultaneous activity by OSHA to develop a generic hazard communication standard. This proposal would require manufacturers to provide information to downstream users about the chemicals and chemical mixtures transmitted to them. The dangers associated with various workplace chemical products would be conveyed to workers in a simple, efficient, and effective manner.

The chronology of events leading to OSHA's proposal for a Hazard Communication Standard is as follows:

1974 - OSHA established a Standards Advisory Committee for, and NIOSH issued a criteria document on, labeling of hazardous materials.

1976 - The House Government Operations Subcommittee on Manpower and Housing issued a report recommending that OSHA require manufacturers to disclose to employers and their employees any toxic ingredients in their products.

1979 - (January) OSHA issued an Advance Notice of Proposed Rulemaking on chemical labeling (42 FR 5372).

1981 - (January) OSHA [redacted] issued a labeling proposal.

1981 - (February) OSHA withdrew the January, 1981, proposal for review.

1982 - (March) OSHA issued an Advance Notice of Proposed Rulemaking on a Hazards Communication Standard.

1983 - (May) Projected Final Rule Date.

Mr. GORE. The earlier panel indicated that we need to be paying more attention to these hazards and getting better data. It seems like you are proposing to move backward in this area and allow us to have less data, substantially less.

Dr. VANCE. I think that the hazard communications standard which OSHA proposes to put into place will result in substantial information on reproductive hazards being transmitted to employees, and I think it will result in the acquisition of that kind of information——

Mr. GORE. But that is already in effect, right?

Dr. VANCE. No. That is a proposal, it is not in effect.

Mr. GORE. But the proposal has been in process for quite some time, and what you are doing is modifying the proposal; is that right?

Dr. VANCE. There is a distinction to be made, Mr. Chairman. OSHA has an existing access to medical records standard.

Mr. GORE. Yes.

Dr. VANCE. OSHA is proposing to modify that existing standard. At the same time, there is simultaneous activity going on. This other activity is a proposal to develop a generic hazard communications standard. There are two proposals out.

Mr. GORE. But that has been in the works for years, right?

Dr. VANCE. The proposed hazard communications standard, in one form or another, for several years, yes. But the actual draft standard on which comment is being received now has been out for the last several months. That is in public hearing today.

Mr. GORE. The proposed regulation also shortens the length of time for which exposure records must be kept; is that correct?

Dr. VANCE. That is correct.

Mr. GORE. Why?

Dr. VANCE. The process of maintaining and keeping records, obviously, is a burden to be maintained by whoever it is that has to maintain those records. It is not reasonable to maintain records unless there is some utility for maintaining those records.

Mr. GORE. We have heard from earlier panels about the research needs with respect to reproductive hazards. The key role played by retrospective epidemiological analyses, if you don't have the exposure records, you can't do those analyses.

Dr. VANCE. Absolutely right, Mr. Chairman. Those kinds of comments would be exactly the kinds of comments that we would solicit and that we would expect to receive from the interested scientific community in response to the request for comments on the proposed access to medical records standard. I am sure that comments along those direct lines will come in, and that they will be evaluated fairly, fully and completely.

Mr. GORE. So it is kind of a trial balloon that you don't think is likely to fly?

Dr. VANCE. It is not fair to say that. There is an actual judicial process that goes on within the agency. When the agency puts out a proposal, the decision ultimately comes down on the basis of the evidence submitted in the record and on the comment that comes in from the public. Every one of those comments is evaluated very carefully.

In order to make a change in the standard, obviously substantial evidence supporting that change will have to be submitted.

Mr. GORE. Why don't you go the other way and let the industry object? If your own work shows you that you need the data for the retrospective epidemiological work, it seems to me that you go that route instead of shortening the period and then waiting for the scientific community to yell about it.

Dr. VANCE. I understand your point, but, in fact, we do have a statutory requirement that we do review our regulations from time to time. The Regulatory Flexibility Act, I am sure you and your staff are familiar with. Time-to-time regulation review is a part of the process that the agencies do have to deal with.

Mr. GORE. Nobody forced you to do this. Nothing forces you to change it. We all know what is involved here. I just hope that you will take into consideration the fact that the scientific community is just beginning to develop a useful body of data and a useful methodology for helping American men and women avoid this tragedy of reproductive hazards. The only way that this science can advance is with the information that it needs to progress as rapidly as we have seen in the field of carcinogenesis analysis.

With respect to the identification and labeling of hazardous materials in the workplace, at what stage is OSHA's effort to issue a regulation in final form addressing this problem?

Dr. VANCE. I would say that we are somewhere between 9 and 15 months from that. The proposed standard has been submitted for public comment, and there has been a huge amount of public comment. As I recall, in the very first stages of it about a month ago, we got some 200 comments back.

The conclusion of those hearings will take place in Detroit on Friday of this week. As soon as that is complete, the staff will begin work on those comments, digesting them, categorizing them, classifying them, evaluating them. From there, it is simply a matter of time until we get the final standard. But the preliminary work necessary to getting the standard done, the notices and that kind of things, that will be completed on Friday of this week.

Mr. GORE. Can you tell us whether the OSHA hazardous chemical labeling proposal will require a warning to employees of possible reproductive hazards?

Dr. VANCE. I can't say that it will; it may.

Mr. GORE. Does the proposal contain it?

Dr. VANCE. The proposal requires that an employer make available information on hazards of the chemicals that are in the workplace to the employees. That employer also has to do a hazard evaluation. If the hazard evaluation shows the existence of reproductive hazards among the other universal hazards that exist with that particular substance, then the employer has to make that information available to the employee. The employer has to do his own hazard evaluation.

Mr. GORE. Including an evaluation of reproductive hazards?

Dr. VANCE. Yes.

Mr. GORE. So you sort of leave it up to them to define and identify the hazards involved with the chemicals that their workers are exposed to.

Dr. VANCE. It is a performance-oriented standard. That is one element of it, yes, Mr. Chairman.

Mr. GORE. I won't be surprised if they miss a few.

Let me move on to ethylene oxide. In your opinion, what kind of reproductive health hazard does ethylene oxide pose?

Dr. VANCE. We have heard a fair amount of testimony on it here today. I have discussed ethylene oxide with my staff. We are involved in an active rulemaking process with that. We heard testimony today on chromatid exchange. It is an animal teratogen. It definitely is a candidate for regulatory action, certainly based just on the reproductive hazards associated with it alone, if not for the rest of the hazards. We are engaged in a rulemaking process on ethylene oxide at this time, and we are drafting a standard at this time.

Mr. GORE. I see. What is your tentative conclusion about it? Is it that it does pose a reproductive health hazard?

Dr. VANCE. Well, that it may. I think that is the kind of thing that we have asked for comment on, and we have put out an advance notice of proposed rulemaking which we have asked for comment on. I am not sure what the scope of the comments were. I am certainly prepared to say that it may well be a reproductive hazard.

Mr. GORE. When did you come to that conclusion? When did OSHA come to that conclusion?

Dr. VANCE. I think that the advanced notice of proposed rulemaking itself shows that it may be a reproductive hazard. You look at the notice that OSHA issued in the Federal Register soliciting comment, that, in and of itself——

Mr. GORE. When was that?

Dr. VANCE. I don't have the date readily in mind.

Mr. GORE. Do you know roughly when OSHA came to the conclusion that there was a risk that this may be a reproductive hazard?

Dr. VANCE. I don't know the date. I will be glad to supply you any information that we may have concerning the nature and kind of information that we received on that element of your question.

Mr. GORE. OK.

[The information follows:]

In December 1980, OSHA became aware of a study of chronic inhalation of ethylene oxide (EtO) in rats that had been performed at the Bushy Run Laboratory of Union Carbide Corporation. In the months that followed, OSHA's staff reviewed the literature on EtO and found that there was evidence of apparent reproductive changes induced by EtO.

The preliminary risk assessment of the hazards of EtO indicate that the greatest hazard may be its effect on the blood forming system rather than its reproductive effects. This is because the neoplastic changes (leukemia, and to a lesser extent mesothelioma) in experimental animals (rats) occur at a lower airborne concentration of EtO than do the reproductive effects (early fetal death—probably a dominant lethal effect).

The chromosomal effects reported by Johnson and Johnson is response to our ANPR of January 26, 1982, appear to support the concept that the blood forming organs (bone marrow) may be the target organ.

Mr. GORE. We have information that it was almost a year ago, September 1981.

Two studies on ethylene oxide exposure summarized by OSHA showed that chromosome damage resulted; are you familiar with that?

Dr. VANCE. I know that the studies exist. In fact, the member of the staff who handles that material on a day-to-day basis is here today, Dr. Beliles. If you would prefer to ask some specific questions on the detailed technical nature of the studies that have been done on ethylene oxide, I would be happy to ask him—or you, of course, Mr. Chairman, could ask him questions.

Mr. GORE. Thank you. I will ask the staff of the subcommittee to communicate with him.

Based on the evidence available indicating the potential health risk of ethylene oxide, what was the staff recommendation at OSHA?

Dr. VANCE. To adopt a standard lowering the permissible exposure limit.

Mr. GORE. When was that?

Dr. VANCE. We made the recommendation to the Deputy Assistant Secretary 2 or 3 weeks ago.

Mr. GORE. When?

Dr. VANCE. Within the last 3 weeks.

Mr. GORE. I see.

When did the staff recommend a standard?

Dr. VANCE. At that time, to the best of my knowledge.

Mr. GORE. Was there an earlier recommendation from staff?

Dr. VANCE. Not to my knowledge.

Mr. GORE. Who is your technical expert?

Dr. VANCE. Dr. Beliles.

Mr. GORE. If you could come forward and have a seat, please. Welcome. Identify yourself to the reporter, if you would.

Dr. BELILES. I am Robert Beliles. I am Director of the Office of Carcinogenics.

Mr. GORE. Was there an earlier staff recommendation for an emergency temporary standard or a regular standard?

Dr. BELILES. The agency was petitioned to adopt an emergency temporary standard on ethylene oxide.

Mr. GORE. When?

Dr. BELILES. It seems to me that it was about last October or November, if I recall. The Assistant Secretary determined largely because industry had lowered voluntarily——

Mr. GORE. Wait a second. You are referring to the petition?

Dr. BELILES. Yes, sir.

Mr. GORE. You said you were petitioned. But back in August of 1981, Mr. Auchter said that OSHA is currently considering a request for issuance of an emergency temporary standard for ethylene oxide. My question is, When did the staff recommend such a standard, if it did? First of all, did it?

Dr. BELILES. The petition for an emergency temporary standard was denied. The staff at the time of the denial recommended—at least as far as I know, the staff of OSHA is quite large—but we recommended when it was denied that we issue an ANPR and consider lowering the current exposure level.

Mr. GORE. Prior to the denial, did the staff recommend an emergency temporary standard?

Dr. BELILES. I really don't know. I believe that that activity was handled by Dr. Hayes Bell in Tech Support, and he is no longer with the agency.

Mr. GORE. The understanding of the subcommittee is that the staff did recommend either an emergency temporary standard or regular standard. From that time, in the fall of 1981, through a couple of weeks ago, nothing happened; is that correct?

Dr. BELILES. No, sir. We issued an ANPR and solicited comment.

Mr. GORE. When did you issue that?

Dr. BELILES. I think that was January 26, 1982. We have received comments and information on the technological and economic feasibility. We have an idea of what industry's current exposure levels are. We have had a very interesting report from Johnson & Johnson on chromosome aberrations in workers. We are in the process of developing a standard at the present time.

Mr. GORE. It is true that NIOSH recommended in the spring of 1981 that the standard be lowered from 50 parts per million to 1 part per million?

Dr. BELILES. I believe that is correct.

Mr. GORE. Could you give us your timetable on action on this? What should one expect on it?

Dr. VANCE. May I respond to that, Mr. Chairman, because that is very much a policy type question.

To process the promulgation of the standard at OSHA involves of course the scientific information which we put in the health standards directory. It also involves a regulatory analysis. It involves policy and legal input from the Solicitor of Labor's Office and from our Policy Office.

It is not possible to precisely define the amount of time that it takes to put out any of our standards. I think that something in the nature of a year would be a reasonable guess.

Mr. GORE. It has been a year. Are you talking about another year?

Dr. VANCE. From today. I think that that would be a reasonable guess.

[The following information was subsequently supplied for the record:]

Comprehensive health standards take a long time to develop—from two to three years. For example:

Carcinogen Policy: Proposed regulation published 10/14/77. Final standard issued 1/22/80.

Lead: Proposed regulation published 10/3/75. Final standard issued 11/4/78.

Arsenic: Proposed regulation published 1/21/75. Final standard issued 5/5/78.

Mr. GORE. Well, I have known for a year that a standard was in prospect and staff recommended an emergency standard, and yet it is going to be another year after this.

You tell me if I am wrong, but from the point of view of people exposed to it, doesn't that seem as if they are not getting the kind of action that they have a right to expect, or am I going wrong there?

Dr. VANCE. Well, as testimony indicated, one of the reasons why the emergency temporary standard wasn't adopted was because a major fraction of the work force is not exposed at a level anywhere close to where the present 50 parts per million permissible exposure limit is. Most people are exposed at a level below that.

So, it is not fair to say that the majority of the people who were exposed to ethylene oxide are exposed at concentrations comparable to the PEL. The process of promulgating a regulation is in large as involved as it is because virtually every standard that OSHA adopts, Mr. Chairman, is likely to end up in litigation.

If we don't do the job right, don't make sure that the scientific basis is there and all the legal basis is in, we will just end up with a situation such as what happened with benzene. It is going to be overturned by the courts. We have to do it right. We have to dot the i's and cross the t's, do all of the required scientific and economic and all of the legal analysis that has to go into one of these things.

Mr. GORE. We would like to see that exposure data that you referred to, if you could submit that.

Dr. VANCE. Surely.

[The information follows:]

Following receipt on August 13, 1981, of a petition for issuance of an emergency temporary standard for ethylene oxide (EtO), I directed OSHA staff to investigate the petitioners' claim that an emergency existed in the workplace because of EtO exposure. In the course of this investigation, staff assembled an administrative record of over 200 documents which included some exposure data for US workers. These data, while preliminary and incomplete, did not support issuance of an emergency temporary standard.

In an affidavit presented on October 22, 1982, in *Public Citizen Health Research Group, et al.,* v. *Thorne G. Auchter, et al.,* in the D.C. District Court, the following is stated: . . . the available data on worker exposure to EtO showed that exposures were generally far below the 50 ppm [parts per million] level [of OSHA's existing standard]. Thus in EtO production and industrial use, the exposures were below 5 ppm over an 8-hour day. In the health care and hospital fields, the data on 8-hour expsoures were predominantly at or near 10 ppm. The evidence indicated, further, that in some cases these low exposure values were the result of voluntary actions on the part of employers with exposed employees acting responsibly to reduce chronic exposure levels . . .

On the basis of these preliminary data on employee exposure, as well as lack of direct evidence "documenting a statistically significant excess risk of cancer in humans from EtO chronic inhalation exposures below approximately 14 ppm TWA" (8-hour time-weighted average) and lack of direct evidence of the feasibility of various means of exposure control, OSHA staff recommended to me on September 28, 1981, that an emergency temporary standard not be issued. Staff recommended at that time that OSHA issue an immediate Advance Notice of Proposed Rulemaking (ANPR) "to examine the need to revise the 50 ppm standard through normal rulemaking processes." As a result of that ANPR of January 26, 1982, OSHA has sought additional information about employee exposure to EtO, which, while still incomplete, appears to confirm the earlier conclusions outlined above.

Mr. GORE. Let me ask a question of FDA.

What, in your opinion, is the reliability of animal models in predicting teratogenic effects in humans?

Dr. FLAMM. I am sure that there is room here for a lot of honest disagreement among scientists who vary in their judgments as to how good the predictability is. I think some progress has been made in this area, particularly coming out of the IRLG workshop that we had mentioned earlier, where there is some reason to believe that the predictability of maternal toxicity versus developmental toxicity from one species to another is really quite good.

If that indication holds up as more substances are tested in the laboratory, I think we will see in the coming years a greater reliance upon the ratio of developmental to maternal toxicity as a way of getting at what the human risk might be from a particular teratogen or developmental toxin.

Mr. GORE. Let me thank you all for coming here and apologize for the length of the proceeding. Let me conclude by saying that it appears, as a result of our inquiry, that a good deal more should be done to better identify and quantify the hazards that Americans face in the area of reproductive hazards.

I want to thank all of our witnesses today in helping us in this inquiry. Thank you very much.

The hearing is adjourned.

[Whereupon, at 2:35 p.m. the subcommittee was adjourned.]

APPENDIX

Lilly Research Laboratories
A Division of Eli Lilly and Company
307 East McCarty Street
Indianapolis, Indiana 46285

E. F. Alder
Vice President

August 19, 1982

The Honorable Albert Gore, Jr., Chairman
The Honorable Robert S. Walker, Ranking
Minority Member
Subcommittee on Investigations and
Oversight
Committee on Science and Technology
U. S. House of Representatives
Washington, D. C. 20515

Gentlemen:

During the hearings of your Subcommittee held on July 27, 1982 for the purpose of determining the status of detection and prevention of chemical and environmental hazards to human reproduction, one of our products, Surflan (oryzalin, Elanco), was discussed.

At the hearing you requested from EPA copies of two teratology studies on oryzalin which were conducted by our company. We welcome your review of these studies. There are, however, a total of eight studies containing reproductive data which have been conducted on oryzalin.

We would like to offer you the opportunity to review other reproductive data on oryzalin. To make this review possible, we have suggested that EPA submit to you data on the six additional studies. We hope that any judgment made on oryzalin will be on the basis of the complete data package and firmly believe that your review of these data will alleviate any anxieties or concerns you may have regarding this chemical.

We have prepared a brief statement which accompanies this letter and we respectfully request that this letter and the statement be included as part of the hearing record.

Very truly yours,

Edwin F. Alder

Edwin F. Alder, Ph.D.
Vice President

ths

Attachment

STATEMENT OF ELANCO PRODUCTS COMPANY
PRESENTED TO THE SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT OF THE
COMMITTEE ON SCIENCE AND TECHNOLOGY

Elanco Products Company is submitting this statement for the record in response to the testimony regarding the product Surflan® (oryzalin, Elanco) which was discussed during Subcommittee hearings on July 27, 1982. We specifically would like to respond to the issue of oryzalin effects on reproduction. There are comprehensive toxicology data in laboratory animals as well as data assembled from a review of medical records of all persons who have been involved in the manufacturing of oryzalin that bear on this issue.

Oryzalin is a herbicide to control weeds in soybeans, trees and vines and certain other crops. It has been marketed since 1974 by Elanco, a Division of Eli Lilly and Company.

Toxicology Studies in Laboratory Animals

A total of eight studies to determine possible reproduction effects have been conducted in the laboratories of Eli Lilly and Company. Six of the studies were conducted on oryzalin and two on the proximate intermediate in oryzalin manufacture.

In four teratology studies, two in rats and two in rabbits*, large daily doses of oryzalin were given to pregnant animals during the critical period of fetal development. Examination of offspring did not provide evidence of an adverse effect of the treatment.

(*The two rabbit studies which were requested from EPA by Chairman Gore during the hearings are included in these studies. When our interpretation of one of the studies was questioned by EPA, we engaged two consultants, each with an international reputation in teratology research, to conduct independent reviews of the study. Both experts agreed with Lilly scientists that there was not sufficient

evidence to conclude that oryzalin produced a teratogenic effect in the rabbit. However, at EPA's request, Lilly did repeat the study. The second study confirmed our original conclusion that the compound had no adverse effects on fetal development in the rabbit. The EPA has reviewed the second study and is in agreement with our conclusion.)

In a rat multigeneration study on oryzalin, there were 1,141 offspring examined and no treatment related abnormalities were found. Other animal studies indicated no adverse effects on spermatogenesis or fertility nor were there any teratological effects from exposure to the proximate intermediate of oryzalin.

In summary, a comprehensive investigation of oryzalin has been done to assess the potential for the compound to produce adverse effects on the reproduction of laboratory animals. Large daily doses given to animals were tolerated with no effect on fertility, fetal development or survival and health of the offspring.

Review of Medical Records of Production Workers

Lilly began a review of medical records of production workers in all plants where oryzalin had been or was being formulated or manufactured immediately after hearing about the birth defect problem at the GAF Corporation plant in Rensselaer, New York. Since manufacturing began there in 1973, oryzalin has been handled in eight (8) different plant sites, including the GAF facility. Oryzalin was produced in the GAF plant for about eighteen months during 1975 and 1976. During this time, according to EPA's investigation report, there were approximately sixty (60) other chemicals produced in the same plant.

Lilly conducted a thorough investigation of medical records of those who were engaged in oryzalin production in the other seven plants. There were fifty-one (51) births recorded, born to workers exposed to oryzalin during the period 1973-1980, none with heart defects. Only about 3 percent of the total oryzalin produced to date was manufactured at the GAF plant.

Therefore, the opportunity for exposure in other facilities has been far greater than at the GAF plant. However, there have been no similar incidences of birth defects.

Extensive investigations initiated by EPA, OSHA and NIOSH have been conducted. Lilly continues to maintain a surveillance of medical records in plants where oryzalin is still being handled. To the best of our knowledge, there is no other evidence to support the allegations originating from the GAF, New York plant.

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E.F.A.
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